ClinicalEvidence

Malaria: prevention in travellers

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ABSTRACT

INTRODUCTION: Malaria transmission occurs most frequently in environments with humidity greater than 60% and ambient temperature of 25 °C to 30 °C. Risks increase with longer visits and depend on activity. Infection can follow a single mosquito bite. Incubation is usually 10 to 14 days but can be up to 18 months depending on the strain of parasite. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of non-drug preventive interventions in non-pregnant adult travellers? What are the effects of drug prophylaxis in non-pregnant adult travellers? What are the effects of antimalaria vaccines in adult and child travellers? What are the effects of antimalaria interventions in child travellers, pregnant travellers, and in airline pilots? We searched: Medline, Embase, The Cochrane Library, and other important databases up to November 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 79 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: aerosol insecticides, amodiaquine, air conditioning and electric fans, atovaquone–proguanil, biological control measures, chloroquine (alone or with proguanil), diethyltoluamide (DEET), dietary supplementation, doxycycline, electronic mosquito repellents, full-length and light-coloured clothing, insecticide-treated clothing/nets, mefloquine, mosquito coils and vapourising mats, primaquine, pyrimethamine–dapsone, pyrimethamine–sulfadoxine, smoke, topical (skin-applied) insect repellents, and vaccines.

QUESTIONS

INTERVENTIONS

NON-DRUG PREVENTION IN ADULT TRAVELLERS

Likely to be beneficial

Unknown effectiveness

DRUG PROPHYLAXIS IN ADULT TRAVELLERS

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

Likely to be ineffective or harmful

Footnote

*Categorisation based on consensus.

Key points

- Malaria transmission occurs most frequently in environments with a humidity greater than 60% and ambient temperature of 25 °C to 30 °C. Risks increase with longer visits, and depend on activity.

  Infection can follow a single mosquito bite. Incubation is usually 10 to 14 days, but can be up to 18 months depending on the strain of parasite.

  Complications are usually due to delayed or inappropriate treatment, but up to 88% of previously healthy travellers recover fully with prompt treatment. Older people have a worse prognosis.
- Many of the studies on prevention of malaria have been performed on people other than travellers, such as residents of endemic malaria areas.
- Various non-drug preventive measures may be effective, but some may have adverse effects.

  There is a consensus that skin-applied chemical repellents containing DEET (diethyltoluamide) reduce the risk of insect bites. Picaridin is a newer and possibly more effective repellent than DEET, but it has not yet been evaluated against clinical outcomes.

  Using treated nets or clothing may be beneficial.

  Long-lasting insecticidal nets (LLINs) are likely to have an extended duration of action compared with conventionally treated bed nets.

  We don't know whether insecticide sprays, or lifestyle changes such as wearing full-length clothing, dietary supplementation, use of air conditioning or electric fans, mosquito coils or vapourising mats, bath or chemical base oils, skin-applied plant-based repellents, electronic mosquito repellents, outdoor smoke, vaccines, or biological control measures can reduce the risk of malaria infection. Mosquito coils and vapourising mats should not be used indoors.
- Various drug treatments may be effective in preventing malaria, but we cannot be sure which is the most effective drug regimen, and most have adverse effects that can sometimes be serious.
- Resistance to individual drugs varies between geographical areas and also over time at the same location. Travellers should be guided by the most up-to-date information on resistance patterns and recommendations for drug prophylaxis for the area that they are travelling to.

  Atovaquone–proguanil and doxycycline may be beneficial, and doxycycline protects against other travel-associated infections besides malaria.

  Chloroquine is considered to reduce the risk of malaria in travellers to areas where chloroquine resistance is low, although we found few studies.

  Mefloquine and chloroquine–proguanil may be beneficial, but their adverse effects (including neuropsychiatric adverse events, in the case of mefloquine) must also be considered.

  We don't know whether pyrimethamine–dapsone or pyrimethamine–sulfadoxine are effective.

Children may be at risk of encephalopathic adverse effects from topical insect repellents containing DEET. There is consensus that chloroquine is effective and safe in preventing malaria in children, but we don't know whether this is the case for any other treatments.

- Insecticide-treated bed nets may be effective in preventing malaria in pregnant women.

  We found no RCT evidence about insecticide-treated clothing in pregnant women, but evidence in non-pregnant adults that it is effective is likely to be generalisable to pregnant women. However, there are attendant risks.

  There is consensus that chloroquine may be beneficial in pregnant women.

- Atovaquone–proguanil may have no more adverse effects than placebo in airline pilots, but we have no direct evidence assessing whether treatments are safe or effective in this occupational group. There is no reason to suggest that evidence of benefit of atovaquone–proguanil, chloroquine, or doxycycline in other adults would not be generalisable to airline pilots.

- CAUTION

  Adverse effects of primaquine and amodiaquine limit their use in preventing malaria.

DEFINITION

Malaria is an acute parasitic disease of the tropics and subtropics, caused by the invasion and destruction of red blood cells by one or more of four species of the genus *Plasmodium: P falciparum, P vivax, P ovale*, and *P malariae*. [1] The clinical presentation of malaria varies according to the infecting species, and according to the genetics, immune status, and age of the infected person. [2] The most severe form of human malaria is caused by *P falciparum*, in which variable clinical features include spiking fevers, chills, headache, muscular aching and weakness, vomiting, cough, diarrhoea, and abdominal pain; other symptoms related to organ failure may supervene, such as acute renal failure, generalised convulsions, and circulatory collapse, followed by coma and death. [3] [4] *P falciparum* accounts for greater than 50% of malaria infections in most East Asian countries, greater than 90% in sub-Saharan Africa, and almost 100% in Hispaniola. [5] Travellers are defined here as visitors from a malaria-free area to a malaria-endemic area, who stay in the endemic area for less than 1 year.

INCIDENCE/ PREVALENCE

Malaria is the most dangerous parasitic disease of humans, infecting about 5% of the world's population, and causing about one million deaths each year. [6] The disease is strongly resurgent, owing to the effects of war, climate change, large-scale population movements, increased breeding opportunities for vector mosquitoes, rapidly spreading drug and insecticide resistance, and neglect of public-health infrastructure. [1] [7] Malaria is currently endemic in more than 100 countries, which are visited by more than 125 million international travellers each year. [4] Cases of malaria acquired by international travellers from industrialised countries probably number 25,000 annually. Of these, about 10,000 are reported and 150 are fatal. [8]

AETIOLOGY/ RISK FACTORS

Humans acquire malaria from sporozoites transmitted by the bite of infected female anopheline mosquitoes. [9] Of about 3200 mosquito species so far described, some 430 belong to the genus *Anopheles.* Of these, about 70 anopheline species are known to transmit malaria, with about 40 species considered important vectors. [10] When foraging, blood-thirsty female mosquitoes fly upwind searching for the scent trail of an attractive host. [11] Female anophelines are attracted to their human hosts over a range of 7 to 20 m, through a variety of stimuli, including exhaled carbon dioxide, lactic acid, other host odours, warmth, and moisture. [12] Larger people tend to be bitten by mosquitoes more than smaller individuals. [12] [13] Women receive significantly more mosquito bites in trials than men. [14] Children secrete lower levels of chemical attractants than adults, and therefore usually receive fewer mosquito bites than adults. [15] Malaria transmission does not usually occur at temperatures less than 16 °C or greater than 35 °C, or at altitudes greater than 3000 m above sea level at the equator (lower elevations in cooler climates), because sporozoite development in the mosquito cannot take place. [16] The optimal conditions for transmission are a humidity of greater than 60%, and an ambient temperature of 25 °C to 30 °C. [17] Most of the important vectors of malaria breed in small temporary collections of fresh surface water exposed to sunlight and with little predation, and in sites such as residual pools in drying river beds. [18] Although rainfall provides breeding sites for mosquitoes, excessive rainfall may wash away mosquito larvae and pupae. [19] Conversely, prolonged droughts may be associated with increased malaria transmission if they reduce the size and flow rates of large rivers sufficiently to produce suitable *Anopheles* breeding sites. [20] Anopheline mosquitoes vary in their preferred feeding and resting locations, although most bite in the evening and at night. [21] The *Anopheles* mosquito will feed by day only if unusually hungry. [22] *Anopheles* adults usually fly not more than 2 to 3 km from their breeding sites, although a flight range of up to 7 km has been observed. [23] One cross-sectional study of about 7000 children under the age of 10 years found that, during months of peak transmission, living within 3 km of an *Anopheles* breeding site significantly increased the risk of malaria compared with living 8 to 10 km away (RR 21.00, 95% CI 2.87 to 153.00). [24] Very occasionally, strong winds may carry *Anopheles* up to 30 km or more. [12] In travellers, malaria risk is related to

destination, activity, and duration of travel. A retrospective cohort study (5898 confirmed cases) conducted in Italian travellers between 1989 and 1997 found that the malaria incidence was 1.5/1000 for travel to Africa, 0.11/1000 for travel to Asia, and 0.04/1000 for travel to Central and South America. [25] A survey of approximately 170,000 Swedish travellers found that the prevalence of malaria was lowest among travellers to Central America and the Caribbean (0.01/1000), and higher among travellers to East, Central, and West Africa (prevalence among travellers to East Africa 2.4/1000, Central Africa 3.6/1000, and West Africa 3.0/1000). [26] A survey of 2131 German travellers to sub-Saharan Africa found that solo travellers were at almost a ninefold greater risk of infection than those on package tours. [27] A case control study (46 cases, 557 controls) reported that a visit to the tropics for more than 21 days doubled the malaria risk compared with visits lasting 21 days or less. [28]

PROGNOSIS

Malaria can develop after just one anopheline mosquito bite. [29] Long-term residents of malaria-endemic areas acquire partial immunity to infected mosquito bites, with only a small proportion of such bites progressing to a new infection (in children aged 6 months to 6 years, monitored for 18 months in western Kenya, only 7.5% of infected bites produced a clinical episode of malaria). [30] In non-immune travellers, the likelihood of malaria infection after a single infected bite is much higher (US marines who spent 1–14 nights in Liberia experienced a 44% malaria acquisition rate). [31] Human malaria has a usual incubation period that ranges from 10 to 14 days (*P falciparum*, *P vivax*, and *P ovale*) to about 28 days (*P malariae*). [32] Certain strains of *P vivax* and *P ovale* can have a much longer incubation period of 6 to 18 months. [20] About 90% of malaria attacks in travellers occur at home. [33] About 36% of cases that develop after returning home do so more than 2 months after the traveller's return. [34] People returning from an endemic area with any fever pattern should be considered to have malaria until proved otherwise. [4] [6] [22] [29] [35] Once malaria infection occurs, older travellers are at greater risk of poor clinical outcomes and death. In US travellers between 1966 and 1987, the case fatality rate was 0.4% for people aged 0 to 19 years, 2.2% for ages 20 to 39 years, 5.8% for ages 40 to 69 years, and 30.3% for those aged 70 to 79 years. [36] Complications and death from malaria are mainly due to inappropriate treatment, or to delayed initiation of treatment. [37] If malaria is diagnosed and treated promptly, about 88% of previously healthy travellers will recover completely. [38]

AIMS OF INTERVENTION

To reduce the risk of infection; to prevent illness and death, with minimal adverse effects of treatment.

OUTCOMES

Rates of clinical malaria and death, and adverse effects of treatment. In the question on pregnancy, we also report on outcomes of pregnancy (including maternal anaemia, fetal loss, birth weight, preterm birth, or perinatal death). Proxy measures include numbers of mosquito bites and rates of mosquito catches in indoor areas. We have reported these proxy outcomes only in the comments section of the appropriate options. One experimental study in rabbits has suggested that *Anopheles stephensi* biting behaviour is not affected by their *P falciparum* infection status. [39] This suggests that numbers of *A stephensi* mosquito bites may be a reasonable measure of *P falciparum* malaria risk in humans.

METHODS

Clinical Evidence search and appraisal November 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to November 2009, Embase 1980 to November 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs, RCTs, cohort studies and case control studies in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. We searched for each intervention versus placebo/no treatment and also versus any other listed option under that question, and reported any studies of sufficient quality that we found. Additional hand searches were performed by the contributor of his own files and the *Journal of Travel Medicine*, *Journal of the Royal Army Medical Corps*, and *Transactions of the Royal Society of Tropical Medicine and Hygiene*. In addition, the contributor identified material through systematic updates of his own Cochrane reviews on malaria, and through meetings and regular contact with experts in the field. This material was used to augment the material identified by *Clinical Evidence* searches. As *Clinical Evidence* was unable to perform a second appraisal of results retrieved by the contributor's search, we may have missed studies that could affect our

overall assessment of the interventions in this review. In addition, *Clinical Evidence* uses a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. **Reporting of studies included:** We have included only studies that reported clinical outcomes (such as clinical malaria or death) in the benefits section of this review. Some studies reported only surrogate outcomes such as mosquito landings or catches. We have reported these studies in the comments section. We have also reported poorer-quality observational studies such as population surveys in the comments section. Wherever possible, we have reported studies of malaria prevention in travellers in the benefits section. However, there is a paucity of good-quality studies undertaken in travellers in some options (e.g., with non-drug interventions), and placebo-controlled studies may be difficult to perform or may be unethical in some circumstances. Where no RCT data were available in travellers, we have included data on other population groups (e.g., migrants, and long-term residents in malaria-endemic areas), as results from these groups may be generalisable to travellers. Where we have included data in people other than travellers, we have explicitly stated this. **Harms:** Antimalaria drugs as prophylaxis, and other methods of prevention, may cause adverse effects that can sometimes be severe. An additional challenge with drug prophylaxis is that drug regimens must be taken scrupulously during travel, and most regimens must then be continued for some weeks after returning from travel. Adverse effects may also cause inappropriate early discontinuation of drug prophylaxis, which may result in people developing malaria. Hence, the potential adverse effects of prophylaxis are particularly important. In addition to the *Clinical Evidence* search, data on harms has been augmented by the contributor's own search as outlined above. In addition, some RCTs comparing different drugs did not report on clinical outcomes (clinical malaria) but reported solely on adverse effects. Hence, in some options more RCTs (and analyses based on these RCTs) are reported in the harms section than in the corresponding benefits section. **General reporting:** To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 32).The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of non-drug interventions to prevent malaria in non-pregnant adult travellers?

OPTION AEROSOL INSECTICIDES IN NON-PREGNANT ADULT TRAVELLERS

We found no direct information from RCTs, cohort studies, or case control studies on the effects of aerosol insecticides in preventing malaria in non-pregnant adult travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohort studies, or case control studies on aerosol insecticides in preventing malaria in non-pregnant adult travellers (see comment below).

Harms: We found no studies.

Comment: One large questionnaire survey of 89,617 European tourists returning from East Africa measured malaria incidence with a two-stage self-completed questionnaire administered during the return flight and again 12 weeks later. [40] It found that commercially available personal aerosol insecticides did not significantly reduce the incidence of malaria (P = 0.55). Two community RCTs in lifelong residents of malaria-endemic settings found that indoor residual spraying of synthetic pyrethroids significantly reduced clinical malaria. [41] [42] The RCTs gave no information on adverse effects. However, the RCTs used either an active case detection (selecting sentinel villages for visiting and testing people with fever for malaria) or a cross-sectional survey (testing children in selected schools in sentinal villages), which was below the 80% follow-up specified for inclusion in this review.

Clinical guide:
Historically, indoor residual spraying has not been recommended for short-stay travellers, and we found weak evidence from a large observational study that aerosol insecticides did not reduce the risk of malaria in travellers. [40] However, we found evidence from RCTs of benefit from indoor

residual spraying of synthetic pyrethroids in preventing malaria in residents of malaria-endemic areas. [41] [42] It is possible that this benefit may also be seen in travellers if the same insecticides are used in the same conditions.

OPTION BIOLOGICAL CONTROL MEASURES IN NON-PREGNANT ADULT TRAVELLERS

We found no direct information from RCTs, cohort studies, or case control studies on the effects of biological control measures in preventing malaria in non-pregnant adult travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohort studies, or case control studies of biological control measures in preventing malaria in non-pregnant adult travellers (see comment below).

Harms: We found no studies.

Comment: One systematic review (search date 1997) identified two cohort studies based on mosquito counts. [43] It found no evidence that growing the citrosa plant, and encouraging natural predation of insects by erecting bird or bat houses, reduced bites to humans from infected anopheline mosquitoes. The only known way to reduce mosquito populations naturally is to eliminate sources of standing water — such as blocked gutters; tree-stump holes; and discarded tyres, cans, and bottles. [43]

Clinical guide:
There is no reliable evidence about the effects of biological control measures in preventing malaria in travellers.

OPTION AIR CONDITIONING AND ELECTRIC FANS IN NON-PREGNANT ADULT TRAVELLERS

We found no direct information from RCTs, cohort studies, or case control studies on the effects of air conditioning or electric fans in preventing malaria in non-pregnant adult travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohort studies, or case control studies on air conditioning or electric fans in preventing malaria in non-pregnant adult travellers (see comment below).

Harms: We found no studies.

Comment: **Air conditioning:** One questionnaire survey of 89,617 European tourists returning from East Africa measured malaria incidence with a two-stage self-completed questionnaire administered during the return flight and again 12 weeks later. [40] It found that sleeping in an air-conditioned room significantly reduced the incidence of malaria (P = 0.04).
Electric fans: One cohort study (6 experimental huts in villages in Pakistan) of various antimosquito interventions found that an electric ceiling fan run at high speed significantly reduced total catches of blood-fed culicine mosquitoes (P less than 0.05). [44] However, it did not significantly reduce total catches of blood-fed anopheline mosquitoes. These studies support the finding that mosquitoes are reluctant to fly in windy conditions, [45] but suggest that anopheline mosquitoes may be more tolerant than culicine mosquitoes of air turbulence.
Clinical guide:
There is weak evidence of possible benefit from air conditioning in preventing malaria in travellers. There is no reliable evidence about the effects of electric fans in preventing malaria in travellers.

OPTION ELECTRONIC MOSQUITO REPELLENTS IN NON-PREGNANT ADULT TRAVELLERS

We found no direct information from RCTs, cohort studies, or case control studies on the effects of electronic mosquito repellents in preventing malaria in non-pregnant adult travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found one systematic review (search date 2009), which found no RCTs reporting clinical outcomes (see comment below). [46] We found no cohort studies or case control studies reporting clinical outcomes (see comment below).

Harms: We found no studies.

Comment: The systematic review included 10 field entomological studies comparing electronic mosquito repellents (EMRs) versus control and reported the number of mosquitoes of any species landing on

exposed body parts of humans acting as baits. [46] Studies were undertaken in North America (7 studies), Africa (2 studies), and Russia (1 study); the studies in North America and Russia being on *Aedes*, *Culex*, *Culiseta*, and *Mansonia* mosquitoes, and the two studies in Africa being on *Anopheles* and other mosquito genera. Only one study was blinded; in the remaining studies there was no blinding or blinding was unclear. The review reported that all 10 studies found that landing rates with and without the EMR were little different and that the EMRs failed to repel mosquitoes (statistical analysis between groups not reported). The review concluded that EMRs are not effective in repelling mosquitoes. [46]

Clinical guide:
There is weak evidence suggesting that electronic mosquito repellents may be of no benefit in preventing malaria in travellers.

OPTION MOSQUITO COILS AND VAPOURISING MATS IN NON-PREGNANT ADULT TRAVELLERS

Malaria prevention
Coil use or vapourising mats compared with no coil use or vapourising mats We don't know whether the use of mosquito coils or vapouring mats is more effective than no mosquito coils or vapourising mats at preventing malaria in travellers or long-term residents in malaria endemic settings (very low-quality evidence).

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits:

Coil use or vapourising mats versus no coil use or vapouring mats:
We found one systematic review (search date 2003) that evaluated the use of coils to prevent malaria. [47] It identified no RCTs. We found no systematic review and no RCTs examining the effect of vapourising mats on the incidence of clinical malaria. We found three case control studies. [28] [48] [49] The first case control study (603 British travellers to the Gambia between September and December, 48% of whom burnt mosquito coils) found that, when assessing people with and without malaria, there was no significant difference in coil use between groups (OR 0.65, 95% CI 0.32 to 1.34). [28] In the second case control study (457 urban residents in southern India, surveyed during the rainy season), about 13% of participants used mosquito coils to prevent malaria, and about 43% used vapourising mats; the use of these devices did not significantly reduce malaria rates (OR 0.85, 95% CI 0.57 to 1.28). The use of other repellent methods such as nets, oils, and creams was included in this final figure. [48] The third case control study (406 village residents in a high-transmission area of southern Laos) found that non-use of a mosquito coil did not increase the risk of malaria acquisition (OR 1.35, 95% CI 0.06 to 2.91; P = 0.38). [49]

Harms:

Coil use or vapourising mats versus no coil use or vapouring mats:
The systematic review found one trial, which reported irritation of the eyes and nose after coil use. [47] The studies in the systematic review [47] and the subsequent case control studies [28] [48] [49] did not report on other potential adverse effects of exposure to the substances emitted by coils or vapourising mats. These potential adverse effects need investigation.

Comment:

One RCT of coils (residential houses in a squatter area in Malaysia) and one observational study (6 experimental huts in villages in Pakistan) of pyrethroid vapourising mats found that these devices reduced numbers of culicine mosquitoes in indoor spaces. [50] [44]

Clinical guide:
There is evidence that mosquito coils and vapourising mats may be of no benefit in preventing malaria in travellers. Because of their unknown safety profile, these devices should not be used indoors.

OPTION OUTDOOR SMOKE IN NON-PREGNANT ADULT TRAVELLERS

We found no direct information from RCTs, cohort studies, or case control studies on the effects of outdoor smoke in preventing malaria in non-pregnant adult travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits:

We found no systematic review, RCTs, cohort studies, or case control studies on outdoor smoke in preventing malaria in non-pregnant adult travellers (see comment below).

Harms:

We found no studies.

Comment:

One controlled clinical trial, in which five small fires were tended on five successive evenings in a village in Papua New Guinea, found a smoke-specific and species-specific effect from different types of outdoor smoke. [51] Catches of one anopheline species were reduced by 84% by burning

betelnut (95% CI 62% to 94%), by 69% by burning ginger (95% CI 25% to 87%), and by 66% by burning coconut husks (95% CI 17% to 86%). There may be an irritant and toxic effect of outdoor smoke on the eyes and respiratory system, but this effect was not quantified in the controlled clinical trial. [51]

Clinical guide:
There is weak evidence of benefit from certain types of outdoor smoke in repelling mosquitoes. This may translate into clinical benefit by reducing bites, which is likely to reduce malaria infection. However, there is currently no evidence about the effects of outdoor smoke on malaria risk in travellers.

OPTION INSECTICIDE-TREATED NETS IN NON-PREGNANT ADULT TRAVELLERS

Mortality
Insecticide-treated nets compared with no nets or untreated nets Bed nets sprayed or impregnated with a pyrethroid insecticide, such as permethrin, may be more effective than no bed nets or untreated bed nets at reducing mortality in children resident in malaria-endemic settings, but we don't know about adults resident in malaria-endemic settings (very low-quality evidence).

Malaria prevention
Insecticide-treated nets compared with no nets or untreated nets Bed nets sprayed or impregnated with a pyrethroid insecticide such as permethrin may be more effective than no bed nets or untreated bed nets at reducing rates of mild episodes of malaria in child and adult residents in malaria-endemic settings (very low-quality evidence).

Note
We found no direct information from RCTs, cohort studies, or case control studies assessing the effects of insecticide-treated bed nets on malaria in non-pregnant adult travellers. Although the evidence we found was in non-traveller children and adults, the results are likely to be generalisable to other groups, such as travellers. Therefore, the evidence suggests that insecticide-treated bed nets are likely to be of benefit in preventing malaria in travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits:

We found no systematic review, RCTs, cohort studies, or case control studies in travellers. We found one systematic review (search date 2003), which identified 21 RCTs in malaria-endemic settings (stable transmission area more than 1 infective bite/person/year; non-traveller children and adults). [52] It found that, over 4 to 29 months, bed nets sprayed or impregnated with a pyrethroid insecticide such as permethrin were associated with lower rates of mild episodes of malaria compared with no or untreated bed nets (insecticide-treated bed nets *v* no nets: 4 RCTs, adults and children [mainly children]; RRR 50%; insecticide-treated nets *v* untreated nets: 3 RCTs, adults and children [mainly children]; RRR 39%, CIs not calculated for either analysis, as the analyses included both cluster and non-cluster randomised trials; 1 RCT in untreated-nets analysis included treated curtains rather than bed nets; absolute numbers not reported for either analysis). [52] The review found that bed nets sprayed or impregnated with a pyrethroid insecticide such as permethrin significantly reduced child mortality (impregnated bed nets *v* no nets: 4 RCTs; RR 0.83, 95% CI 0.76 to 0.90, 1 RCT in analysis included treated curtains rather than bed nets; impregnated nets *v* untreated nets: 1 RCT; RR 0.77, 95% CI 0.63 to 0.95; absolute numbers not reported for either analysis).The review did not report on adult mortality.

We found one subsequent cluster RCT in long-term adult and child residents in India, which compared long-lasting insecticidal nets versus control (see comment below). [53] In total, 22 villages were randomised to receive long-lasting nets (8 villages; 1953 people), untreated nets (9 villages; 2019 people), or no nets (5 villages; 1863 people). Malaria incidence was measured by visits every two weeks to each household with finger-prick blood taken from all individuals reporting fever. The RCT found that long-lasting insecticidal nets significantly reduced malaria incidence compared with untreated nets (P less than 0.01) or no nets (P less than 0.01). It found no significant difference in malaria incidence between the untreated-nets and no-nets groups (P greater than 0.05). [53]

Harms:

The review gave no information on adverse effects. [52] The subsequent RCT surveyed 250 people in the insecticide-treated-nets group, and found transitory complaints lasting for a few hours of skin irritation (4%), itching (8%), and eye irritation (1%). [53]

Comment:

Clinical guide:
When used to treat nets conventionally, permethrin remains active for about 4 months. [29] Mosquitoes are increasingly tolerant of pyrethroid insecticides, and there is some evidence that using a carbamate insecticide (such as carbosulfan) to treat bed nets may deter mosquitoes more effectively than using a pyrethroid insecticide to treat nets. [54] A new generation of bed nets, known as long-lasting insecticidal nets (LLINs), incorporate insecticide into or onto the fibres of the net

during the manufacturing process; these nets have biological activity for the full lifespan of the net, typically 4 to 5 years. [53] Although the systematic review analysing insecticide-treated bed nets was undertaken in non-traveller children and adults, the results are likely to be generalisable to other groups, such as travellers. Therefore, the evidence suggests that insecticide-treated bed nets are likely to be of benefit in preventing malaria in travellers.

OPTION INSECTICIDE-TREATED CLOTHING IN NON-PREGNANT ADULT TRAVELLERS

Malaria prevention

Compared with untreated clothing Permethrin-treated clothing may be more effective than untreated clothing at reducing the incidence of malaria in soldiers or refugees. We don't know whether permethrin-treated uniforms are more effective than placebo-treated uniforms at reducing the incidence of malaria in soldiers patrolling a malaria endemic area who are also receiving chemoprophylaxis (very low-quality evidence).

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review but found three RCTs [55] [56] [57] and one controlled clinical trial. [58] The first RCT (172 Colombian soldiers patrolling a malaria-endemic area for a mean of 4.2 weeks) found that permethrin-impregnated uniforms significantly reduced the incidence of malaria compared with non-impregnated uniforms (3/86 [3%] with impregnated uniforms *v* 12/86 [13%] with non-impregnated uniforms; RR 0.25, 95% CI 0.07 to 0.85). [55] The second RCT (102 refugee households in northwestern Pakistan) found that permethrin-treated wraps and top sheets significantly reduced the risk of falciparum malaria compared with placebo over 4 months (RR 0.56, 95% CI 0.41 to 0.78). [56] The third RCT (198 Somali refugees) found that permethrin-impregnated clothing significantly reduced malaria infection rates over 3 months compared with placebo (proportion infected: 38% with permethrin-treated clothing *v* 66% with placebo; P = 0.0002; absolute numbers not reported). [57] One non-randomised controlled trial (663 non-immune Thai soldiers patrolling a malaria-endemic area for 6 months) found that permethrin-treated uniforms did not significantly reduce the incidence of malaria compared with placebo-treated uniforms (68/249 [27%] with permethrin treated uniforms *v* 118/414 [29%] with placebo-treated uniforms; RR and CI not reported). [58] All participants were given the same chemoprophylaxis throughout the study.

Harms: The first RCT also included an analysis of permethrin-impregnated uniforms compared with non-impregnated uniforms in 286 soldiers patrolling a leishmaniasis-endemic area for a mean 6.6 weeks. [55] It found that 2/229 (1%) participants wearing permethrin-impregnated uniforms experienced irritation and itching. No comparative information was given for soldiers wearing non-impregnated uniforms. Neither the second RCT [56] nor the non-randomised study [58] reported on adverse effects. The third RCT reported that no adverse effects were observed in any of the participants. [57]

Comment: In the first RCT, the entire uniform (hat, shirt, undershirt, trousers, and socks) was treated with a single application of permethrin. [55] All participants were instructed to wear the uniform continuously, day and night, with the sleeves rolled down. Each participant washed his own uniform two or three times during the study, using soap and water. Topical (skin-applied) insect repellents were not used. In the second RCT, the chaddar (a veil or wrap) and top sheets of participants were treated with permethrin 1 g/m^2. In the third study, the uniform shirt and trousers of participants were sprayed evenly at high pressure, until entirely saturated with an emulsion containing 151 mL permethrin in 7.5 L water. [58] Re-treatment was not reported in any of the studies.

Clinical guide:

There is some evidence of benefit from insecticide-treated clothing in preventing malaria. Trials in soldiers may not be generalisable to other travellers, because tourists or business travellers may be less likely than soldiers to wear their impregnated garments continuously.

OPTION LIFESTYLE CHANGES (INCLUDING FULL-LENGTH CLOTHING, LIGHT CLOTHING, BEHAVIOUR MODIFICATION) IN NON-PREGNANT ADULT TRAVELLERS

Malaria prevention

Full-length clothing compared with no full-length clothing Wearing clothes covering the arms and legs may be more effective than wearing clothes not covering the arms or legs at reducing the incidence of malaria; however, evidence was weak (very low-quality evidence).

Note

We found no direct information from RCTs, cohort studies, or case control studies on the effects of light-coloured clothing, or of lifestyle changes (such as not travelling to malaria-endemic regions during the rainy season, or not going outdoors in the evening or night) on preventing malaria in non-pregnant adult travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits:

Full-length clothing versus no full-length clothing:
We found no systematic review or RCTs. We found one non-randomised controlled trial (2 co-located squadrons of US Air Force personnel exposed to malaria for 1 month during World War II, with one squadron wearing long-sleeved shirts and trousers continuously and the other wearing short-sleeved shirts and shorts continuously). [59] The trial found that wearing long-sleeved shirts and trousers significantly reduced the incidence of malaria (2/150 [1%] with long-sleeved shirts *v* 62/150 [41%] with short-sleeved shirts; RR and CI not reported). The trial provided no information on denominators, the design or conduct of the study, statistical analysis, or confounders. We also found one case control study (144 expatriates staying in the Central African Republic for more than 4 months), which found that wearing clothes covering arms or legs in the evening or at night significantly reduced malaria acquisition (OR 0.13, 95% CI 0.02 to 0.65; P = 0.01). [60]

Other lifestyle changes:
We found no systematic review, RCT, cohort studies, or case control studies (see comment below).

Harms:

Full-length clothing versus no full-length clothing:
The studies did not report on harms. [59] [60]

Other lifestyle changes:
We found no studies.

Comment:

Full-length clothing:
We found one large questionnaire survey (89,617 European tourists returning from East Africa), which found that wearing long-sleeved shirts and trousers significantly reduced the incidence of malaria (P = 0.02). [40]

Other lifestyle changes:
Other lifestyle changes include not travelling to malaria-endemic regions during the rainy season (when most malaria transmission occurs) and not going outdoors in the evening or at night.

Clinical guide:
Travellers who take day trips from a malaria-free city to a malaria-endemic region may be at minimal risk if they return to the city before dusk. [61] Some authors suggest wearing light-coloured rather than dark clothing, as insects prefer landing on dark surfaces. [61] [62] However, we found no reliable evidence about the effects of wearing light-coloured clothing. Full-length clothing may prevent malaria in travellers.

OPTION SKIN-APPLIED CHEMICAL REPELLENTS IN NON-PREGNANT ADULT TRAVELLERS

Malaria prevention
Skin-applied chemical repellents compared with no skin-applied chemical repellents Repellent soap may be more effective than placebo lotion at reducing the proportion of people experiencing one or more episodes of Plasmodium falciparum malaria in Afghan refugees in Pakistan, and use of repellent soap may be associated with fewer cases of P falciparum malaria and P vivax malaria in long-term residents of eastern Afghanistan. Repellent soap may be no more effective than no soap at reducing the incidence of malaria over 1 year in long-term residents of rural communities in Ecuador and Peru (very low-quality evidence).

Note
We found no direct information from RCTs, cohort studies, or case control studies on the effects of skin-applied chemical repellents in preventing malaria in non-pregnant adult travellers. Five decades of experience of diethyltoluamide (DEET) have led to consensus that it is effective in preventing malaria in travellers. Picaridin may be a more effective repellent than DEET, but it has not yet been evaluated against clinical outcomes. DEET has been reported to cause systemic and skin adverse reactions, particularly with prolonged use.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits:

Skin-applied chemical repellents versus no skin-applied chemical repellents:
We found no systematic review, RCTs, cohort studies, or case control studies on the effects of skin-applied chemical repellents to prevent malaria in travellers. However, we found two RCTs [63] [64] and one case control study [65] of repellent soap (containing 20% diethyltoluamide [DEET] and 0.5% permethrin) in long-term residents (see comment below). The first RCT, which randomised communities in rural Ecuador and Peru (8272 people over 1 year), found no significant difference in the incidence of malaria between repellent soap and no soap (protective efficacy of repellent soap: 0% in Ecuador and 26% in Peru; reported as not significant). [63] The RCT reported that continuous soap use was only maintained by 50% to 70% of participants. The second RCT (127

Afghan refugee village households in Pakistan, 1148 people, over 6 months) found that repellent soap significantly reduced the proportion of people experiencing one or more episodes of *P falciparum* malaria compared with placebo lotion (23/618 [4%] using repellent soap *v* 47/530 [9%] using placebo lotion; OR 0.44, 95% CI 0.25 to 0.76). [64] The case control study (96 cases of *P falciparum* and *P vivax* malaria, resident in Nangahar province, eastern Afghanistan) found that recalled use of repellent soap about the likely time of infection (10 days before) significantly reduced malaria infection (OR 0.08, 95% CI 0.01 to 0.61; P less than 0.001). [65]

Harms:

General harms:
We found one case series of systemic toxic reactions (confusion, irritability, insomnia) in US national park employees after repeated and prolonged use of DEET. [66] We found 14 case reports of contact urticaria and irritant contact dermatitis (mostly in soldiers) as a result of DEET. [40] The risk of absorption is especially high if DEET is left in the antecubital fossa overnight. [67] DEET also damages leather and some synthetic clothing fibres, and degrades plastics, such as eyeglass frames. [68] Unlike DEET, picaridin is odourless and non-sticky, and does not damage plastics or fabrics; it has shown no evidence of carcinogenicity or teratogenicity in animal studies. [69] [70]

Skin-applied chemical repellents versus no skin-applied chemical repellents:
The first RCT reported that skin irritation was rare. [63] The second RCT reported that one person had skin irritation. [64] The case control study reported that one person described a burning sensation while using the soap. [65]

Comment:

We found one RCT [71] and one field study [72] that reported mosquito counts. The crossover RCT (100 volunteers in Senegal) compared four commercially available repellent formulations versus placebo. [71] Skin-applied chemical repellents included DEET 50% and icaridine (picaridin) 20%, and it also included two different strengths of para-menthane-diol (PMD; 20% and 50%) derived from the lemon eucalyptus plant. The study was conducted on five consecutive nights, and the repellents were applied to the leg (knee to ankle). The RCT found that all the skin repellents significantly reduced biting mosquitoes captured compared with placebo, the effects lasting for 8 hours (any active intervention *v* placebo; P less than 0.05). [71] It found no significant difference in biting mosquitoes captured between any of the active treatment groups. The field study of picaridin in Burkina Faso (more than 49,000 mosquitoes collected, over 96 nights, of which more than 95% were of the *Anopheles gambiae* complex) found that, after 10 hours of exposure, picaridin reduced the number of mosquitoes landing on the test humans compared with DEET (3698 mosquitoes with picaridin *v* 6836 mosquitoes with DEET; significance not reported for this comparison). [72] Neither study reported on adverse effects. [71] [72]

Larger RCTs are needed to compare DEET versus other topical (skin-applied) repellents and placebo in preventing malaria.

Clinical guide:
Five decades of experience of DEET have led to consensus that it is effective in preventing malaria in travellers. Picaridin may be a more effective repellent than DEET, but it has not yet been evaluated against clinical outcomes.

OPTION SKIN-APPLIED PLANT-BASED REPELLENTS IN NON-PREGNANT ADULT TRAVELLERS

We found no direct information from RCTs, cohort studies, or case control studies on the effects of skin-applied plant-based repellents in preventing malaria in non-pregnant adult travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohort studies, or case control studies in non-pregnant adult travellers that assessed the effects of skin-applied plant-based repellents on malaria acquisition rates (see comment below).

Harms: We found no studies.

Comment:

We found one RCT that randomised 860 households (4008 resident adults and children, relative numbers not reported) in the Bolivian Amazon and compared the use of a plant-based repellent (*Eucalyptus maculata citriodon* with a para-menthane-3,8-diol [PMD] concentration of 30%) combined with insecticide-treated bednet versus an insecticide-treated bednet alone. [73] It analysed 15,174 person-months at risk. The RCT found a significant 80% reduction in *P vivax* infections in the repellent-plus-bednet group (univariate regression analysis adjusted for age: incidence rate ratio, 0.20, 95% CI 0.11 to 0.38; P less than 0.001) and a non-significant reduction in *P falciparum* infections (univariate regression analysis adjusted for age: incidence rate ratio, 0.18, 95% CI 0.02 to 1.40; P = 0.10). [73] Numbers of *P falciparum* infections in the RCT were small (7 cases).

We found two RCTs [74] [71] and two very small non-randomised studies [75] [76] that assessed mosquito landings. The first small RCT (unspecified number of adult volunteers in rural India, 683 anopheline mosquitoes collected over 10 nights) found that neem oil mixed at 2% strength in coconut oil applied at about 1800 hours to face, arms, and legs gave better protection against anopheline landing over 12 hours than placebo coconut oil (0 mosquitoes with 2% neem oil *v* 144 mosquitoes with placebo; percentage protection 100%; P value not reported). [74] The second RCT (100 people) found that PMD significantly reduced biting-mosquito counts compared with placebo (see comments of skin-applied chemical repellents in non-pregnant adult travellers, p 10). [71] The first non-randomised study (5 adult volunteers in rural northeast Bolivia, 8855 mosquitoes collected, greater than 80% anopheline, over 25 nights) compared lemon eucalyptus in isopropanol applied at 1830 hours to the legs versus control (baby oil in 10% ethanol). [75] It found that lemon eucalyptus significantly reduced mosquito landing over 4 hours compared with control (97% protection; P value reported as significant). The study also found that 2% neem oil in alcohol did not significantly reduce mosquito landing over 4 hours compared with baby oil in ethanol (2% neem oil 57% protection; reported as not significant). The second non-randomised study (8 adult volunteers in rural India, unspecified number of mainly culicine mosquitoes collected, over 20 nights) found that, when applied at dusk to hands, face, and feet, both 1 mL of *Cymbopogan martinii martinii* var. *Sofia* (palmarosa oil) and *Cymbopogan citratus* (lemon grass oil) each reduced mosquito landing compared with untreated controls from dusk to dawn (palmarosa oil 97.0% protection, lemon grass oil 96.9% protection; P value not reported). [76] Using skin-applied plant-based repellents to prevent malaria may be more acceptable to certain travellers than using chemical repellents, and may also be safer. There is a growing body of evidence that plant-based repellents are effective for this indication.

Clinical guide:
As with chemical repellents, the duration of protection of plant-based repellents depends on a number of factors, including amount of repellent applied, ambient humidity, rate of sweating, etc. Under study conditions, a duration of protection of 11.0 hours has been recorded for both *Cymbopogan martinii martinii* var. *Sofia* (palmarosa oil) and *Cymbopogan citratus* (lemon grass oil). [76]

OPTION BATH OR CHEMICAL BASE OILS IN NON-PREGNANT ADULT TRAVELLERS

We found no direct information from RCTs, cohort studies, or case control studies on the effects of bath or chemical base oils in preventing malaria in non-pregnant adult travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohort studies, or case control studies on the effects of bath or chemical base oils in preventing malaria in non-pregnant adult travellers (see comment below).

Harms: We found no studies.

Comment: We found one non-randomised controlled trial using mosquito landing catches as an outcome. [76] The non-randomised study (8 adult volunteers in rural India, unspecified number of mainly culicine mosquitoes collected, over 20 nights) found that 1 mL of mylol, applied to hands, face, and feet, reduced mosquito landing compared with untreated controls from dusk to dawn (96% protection; P value not reported). [76] The study did not report on the adverse effects of mylol.

Clinical guide:
Bath oils, and possibly chemical base oils, seem to protect against insect biting not by a repellent action, but by forming a physical barrier between the human target and the insect. [77] Using bath or chemical base oils to prevent malaria may be more acceptable to certain travellers than using chemical repellents, and may also be safer. However, there is only weak evidence that these substances are effective for this indication.

OPTION DIETARY SUPPLEMENTATION IN NON-PREGNANT ADULT TRAVELLERS

We found no direct information from RCTs, cohort studies, or case control studies on the effects of dietary supplementation in preventing malaria in non-pregnant adult travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohort studies, or case control studies in non-pregnant adult travellers that assessed effects of dietary supplementation on malaria acquisition rates (see comment below).

Harms: We found no studies.

Comment:

We found three non-randomised controlled trials (reported in 2 papers), which assessed effects on mosquito landing catches. [78] [79] The first non-randomised trial (18 North American adult volunteers, exposed in a sealed room to 100 female *Aedes aegypti* mosquitoes for 10 minutes) found no significant difference in the proportion of mosquitoes biting between 200 mg of thiamine chloride (vitamin B1) daily for 3 days and placebo (proportion of mosquitoes that bit people: 50% with thiamine chloride *v* 38% with controls; P value reported as not significant). [78] The second non-randomised trial (23 North American adult volunteers, glass vial rolled between hands for 2 minutes then vial exposed to 28–32 female *Anopheles stephensi* mosquitoes for 2 minutes, crossover design) found no significant difference in the number of mosquito landings over 4 weeks after crossover between 1 week's treatment with vitamin B complex multivitamin tablet (that included vitamin C) daily and vitamin C 500 mg control (absolute numbers not reported; P greater than 0.9). [79] The second non-randomised trial (17 North American adult volunteers, glass vial rolled between hands for 2 minutes then vial exposed to 28–32 female *Anopheles stephensi* mosquitoes for 2 minutes, crossover design) found no significant difference between vitamin B1 100 mg three times daily for 1 day and vitamin C 250 mg control in the number of mosquito landings over 4 weeks after crossover (absolute numbers not reported; P greater than 0.9 for both interventions *v* control). [79] The studies gave no information on adverse effects. [78] [79]

Clinical guide:

There is evidence that dietary supplementation with vitamin B has no repellent effect on healthy mosquitoes. However, vitamin B1, along with garlic and other dietary and herbal agents, is popularly recommended as malaria prophylaxis. [79] Dietary supplementation to prevent malaria may be more acceptable to some travellers than antimalaria drugs, but there is no evidence that it is effective for this indication.

QUESTION What are the effects of antimalaria drug prophylaxis in non-pregnant adult travellers?

OPTION PRIMAQUINE IN NON-PREGNANT ADULT TRAVELLERS

Malaria prevention

Compared with placebo Primaquine may be more effective than placebo at reducing the incidence of malaria at 16 weeks in non-immune Colombian soldiers (low-quality evidence).

Compared with chloroquine Primaquine may be more effective than chloroquine at reducing P falciparum or P vivax malaria at 16 to 19 weeks in Indonesian males aged 7 to 59 years migrating to an area of chloroquine resistance (very low-quality evidence).

Note

The small risk of severe and possibly fatal haemolysis makes the risk–benefit ratio unacceptable when using primaquine to prevent malaria. Severe haemolytic events have occasionally occurred in trials of primaquine/primaquine analogues, even when the participants had been carefully pre-screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits:

Primaquine versus placebo:

We found one RCT in a military population (176 non-immune Colombian soldiers, aged 18–42 years), which compared primaquine 30 mg daily versus placebo over a 16-week period. [80] It found that the protective efficacy of primaquine was 94% (95% CI 78% to 99%) for *P falciparum* infection and 85% (95% CI 57% to 95%) for *P vivax* infection.

Primaquine versus chloroquine:

We found one non-randomised controlled trial (99 non-immune Indonesian males, aged 7–59 years, migrating to a malaria-endemic setting), which compared primaquine (0.5 mg/kg every 2 days) versus chloroquine (5 mg/kg weekly) over 16–19 weeks in an area of chloroquine resistance. [81] It found that, compared with chloroquine, primaquine significantly reduced *P falciparum* malaria (RR 0.25, 95% CI 0.08 to 0.83; P = 0.014) and *P vivax* malaria (RR 0.10, 95% CI 0.005 to 0.71; P = 0.012).

Primaquine versus atovaquone–proguanil, doxycycline, or mefloquine:

We found one systematic review (search date 2009), which compared primaquine versus atovaquone–proguanil, doxycycline, and mefloquine. [82] The review identified no RCTs.

Harms:

Primaquine versus placebo:

The RCT found that primaquine was associated with severe epigastric pain, abdominal pain, or vomiting in 3/122 (2.5%) people. [80] There were no severe adverse effects with placebo.

Primaquine versus chloroquine:
The non-randomised controlled trial found that primaquine was associated with significantly fewer adverse effects than chloroquine over 16 weeks (total adverse effects: 17 with primaquine *v* 114 with chloroquine; P less than 0.0001). [81]

Primaquine versus atovaquone–proguanil, doxycycline, or mefloquine:
We found no studies.

Comment:

Primaquine can cause acute intravascular haemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and methaemoglobinaemia in people with normal G6PD activity. [80] [81]

Alcohol consumption, other medication, and comorbidities can modify the effects of antimalaria drugs. [83] [84]

Clinical guide:
The small risk of severe and possibly fatal haemolysis makes the risk–benefit ratio unacceptable when using primaquine to prevent malaria. Severe haemolytic events have occasionally occurred in trials of primaquine/primaquine analogues, even when the participants had been carefully prescreened for G6PD deficiency.

OPTION CHLOROQUINE IN NON-PREGNANT ADULT TRAVELLERS

Malaria prevention
Compared with pyrimethamine–sulfadoxine We don't know whether chloroquine and pyrimethamine–sulfadoxine differ in effectiveness at preventing malaria in Austrian industrial workers residing in Nigeria as we found insufficient evidence from one small RCT (very low-quality evidence).

Compared with primaquine Chloroquine may be less effective than primaquine at reducing P falciparum or P vivax malaria at 16 to 19 weeks in Indonesian males aged 7 to 59 years migrating to an area of chloroquine resistance (very low-quality evidence).

Note
P falciparum resistance to chloroquine is now established in most malaria-endemic regions. Chloroquine is a low-cost drug, and decades of experience of using it to prevent malaria in regions where there is no parasite resistance to the drug have led to the consensus that it is effective in travellers to these regions (chiefly Central America and the Near East).

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits:

Chloroquine versus placebo:
We found no systematic review, RCTs, cohort studies, or case control studies in non-pregnant adult travellers.

Chloroquine versus pyrimethamine–sulfadoxine:
One RCT (173 Austrian industrial workers residing in Nigeria; male and female volunteers, immunity status not reported) comparing chloroquine versus pyrimethamine–sulfadoxine found no clinical cases of malaria during prophylaxis after 6 to 22 months. [85] The RCT reported that one participant, who stopped his suppressive medication and left Nigeria, died from falciparum malaria 8 weeks later. [85] The principle aim of the RCT was to examine tolerability and adverse effects. It may have been underpowered to detect clinically important differences between groups in the occurrence of malaria.

Chloroquine versus primaquine:
See benefits of primaquine in adults, p 13 .

Harms:

Retrospective questionnaire surveys have suggested that severe adverse effects from chloroquine are rare at prophylactic dosages. [86]

Chloroquine versus placebo:
We found no studies.

Chloroquine versus pyrimethamine–sulfadoxine:
The RCT found that chloroquine was associated with insomnia in 3/87 (3%) people. [85] Two people withdrew from the study because of adverse effects, one with skin rash and the other with visual disturbance.

Chloroquine versus primaquine:
See harms of primaquine in adults, p 13 .

Comment: Alcohol consumption, other medication, and comorbidities can modify the effects of antimalaria drugs. [83] [84]

Clinical guide:
P falciparum resistance to chloroquine is now established in most malaria-endemic regions, although there are countries (principally in Central America and the Near East) where there has been no reported resistance.

Chloroquine is a low-cost drug, and decades of experience of using it to prevent malaria in regions where there is no parasite resistance to the drug have led to the consensus that it is effective in travellers to these regions (chiefly Central America and the Near East). [87]

OPTION CHLOROQUINE–PROGUANIL IN NON-PREGNANT ADULT TRAVELLERS

Malaria prevention
Compared with chloroquine plus pyrimethamine–sulfadoxine We don't know whether chloroquine–proguanil and chloroquine plus pyrimethamine–sulfadoxine differ in effectiveness at reducing the incidence of P falciparum malaria in travellers to East Africa (very low-quality evidence).

Compared with atovaquone–proguanil We don't know whether chloroquine–proguanil and atovaquone–proguanil differ in effectiveness at preventing malaria in travellers (moderate quality evidence).

Adverse effects
Compared with "standard drugs" Chloroquine–proguanil may be associated with a higher rate of adverse effects or gastrointestinal adverse effects compared with "standard drugs" (results pooled for atovaquone–proguanil, doxycycline, and mefloquine in analysis) in travellers (very low-quality evidence).

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits:

Chloroquine–proguanil versus chloroquine plus pyrimethamine–sulfadoxine:
We found one open-label RCT (767 Scandinavian travellers to East Africa; 70% of trips were longer than 4 weeks; duration of follow-up not reported) comparing chloroquine–proguanil versus chloroquine plus pyrimethamine–sulfadoxine. [88] It found no significant difference between treatments in rates of *P falciparum* malaria (4/384 [1.0%] with chloroquine–proguanil *v* 3/383 [0.7%] with chloroquine plus pyrimethamine–sulfadoxine; RR 1.3, 95% CI 0.3 to 5.9).

Chloroquine–proguanil versus atovaquone–proguanil:
See benefits of atovaquone–proguanil in adults, p 19 .

Harms:

Chloroquine–proguanil versus chloroquine plus pyrimethamine–sulfadoxine:
In the RCT conducted in Scandinavian travellers, adverse effects associated with chloroquine–proguanil were nausea (3%), diarrhoea (2%), and dizziness (1%). [88]

Chloroquine–proguanil versus atovaquone–proguanil:
See harms of atovaquone–proguanil in adults, p 19 .

Chloroquine–proguanil versus "standard drugs":
We found one systematic review (search date 2009), which reported on adverse effects and compared chloroquine–proguanil versus three "standard drugs" (results pooled for atovaquone–proguanil, doxycycline, and mefloquine in analysis). [82] Standard drugs were defined as the main regimens used for travellers to regions with *P falciparum* resistance to chloroquine. The review found that the standard drugs were associated with a significantly lower rate of any adverse effect compared with chloroquine–proguanil (adverse event for which causal relationship between intervention and event is at least a reasonable possibility; 3 RCTs, 1530 people: 218 events with any standard drug *v* 258 events with chloroquine–proguanil; RR 0.84, 95% CI 0.73 to 0.96). It also found that the standard drugs were associated with a significantly lower rate of any gastrointestinal adverse effects compared with chloroquine–proguanil (adverse event for which causal relationship between intervention and event is at least a reasonable possibility; 3 RCTs, 1530 people: 139 events with any standard drug *v* 193 events with chloroquine–proguanil; RR 0.71, 95% CI 0.60 to 0.85). One included RCT was open label; one RCT was in only children while a second was in adults and children; and one RCT had unclear reporting of adverse effects. [82]

Chloroquine–proguanil versus mefloquine:
We found one RCT, [89] which did not report on clinical malaria but reported on adverse effects between treatments (see harms of mefloquine, p 17).

Chloroquine–proguanil versus mefloquine, doxycycline, and atovaquone–proguanil:
We found one RCT, [90] which compared adverse effects of prophylaxis on mood profiles (see harms of mefloquine, p 17).

Comment:

Chloroquine–proguanil is a complex two-drug regimen that is poorly tolerated. [82]

Alcohol consumption, other medication, and comorbidities can modify the effects of antimalaria drugs. [83] [84]

Chloroquine–proguanil versus proguanil alone:
We found one further RCT (1625 Dutch travellers to Africa; 60% spent less than 6 weeks in tropical areas), which compared chloroquine–proguanil versus proguanil alone. [91] It found no significant difference in incidence of *P falciparum* malaria 4 weeks after returning to the Netherlands between chloroquine 300 mg weekly plus proguanil 200 mg daily and proguanil alone (risk per 100 person-months: 2.8, 95% CI 0.9 to 10.1 with chloroquine–proguanil *v* 6.0, 95% CI 2.6 to 14.0 with proguanil alone). One cohort study (470 British soldiers in Belize) found that the risk of mouth ulcers almost doubled with chloroquine–proguanil compared with proguanil alone (P = 0.025). [92] We have not systematically searched for all studies evaluating the effects of proguanil alone in this review. Hence, there may be studies of proguanil alone that we have not identified. However, proguanil alone will be added as a new option to this review at its next update.

Clinical guide:
Chloroquine–proguanil was formerly recommended by some authorities as prophylaxis for travel to regions of *P falciparum* resistance to chloroquine. It is no longer widely used, but it is still occasionally considered for travellers visiting West Africa, and for pregnant women. [82]

OPTION DOXYCYCLINE IN NON-PREGNANT ADULT TRAVELLERS

Malaria prevention
Compared with placebo Doxycycline is more effective than placebo at reducing the risk of malaria after 13 to 20 weeks in non-immune Indonesian soldiers and in Indonesian migrants with limited immunity in a malaria-endemic setting (high-quality evidence).

Compared with mefloquine We don't know whether doxycycline and mefloquine differ in effectiveness at preventing clinical malaria in non-immune soldiers in a malaria-endemic setting (very low-quality evidence).

Adverse effects
Compared with mefloquine Doxycycline may be associated with lower rate of neuropsychiatric adverse events than mefloquine. However, the significance of the result depended on the exact analysis undertaken (low-quality evidence).

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits:

Doxycycline versus placebo:
We found two RCTs. [93] [94] The first RCT (136 Indonesian soldiers, non-immune, exposure approximately 13 weeks) compared doxycycline versus mefloquine versus placebo in a malaria-endemic setting. [93] It found that, in an area of drug resistance, doxycycline significantly reduced the risk of malaria compared with placebo after a prophylaxis period of 13 to 15 weeks (AR: 1/67 [2%] with doxycycline *v* 53/69 [77%] with placebo; RR 0.02, 95% CI 0.003 to 0.14). The second RCT (300 Indonesian migrants with limited immunity) comparing azithromycin versus doxycycline versus placebo found that doxycycline significantly reduced the incidence of malaria compared with placebo over 20 weeks (cases of *P falciparum* malaria: 2/75 [3%] with doxycycline *v* 29/77 [38%] with placebo; RR 0.07, 95% CI 0.02 to 0.29; NNT 3, 95% CI 2 to 4; cases of *P vivax* malaria: 1/75 [2%] with doxycycline *v* 27/77 [35%] with placebo; RR 0.04, 95% CI 0.01 to 0.28). [94]

Doxycycline versus mefloquine:
We found one systematic review (search date 2009), which found two small RCTs in non-immune soldiers. [82] The review found no significant difference between doxycycline and mefloquine in the proportion of people with clinical malaria (1/186 [0.5%] with doxycycline *v* 0/202 [0%] with mefloquine; RR 3.0, 95% CI 0.13 to 73.4). [82] However, there was only one case of malaria in both RCTs, and one RCT only reported results on 253/310 (82%) people enrolled. [82]

Harms:

Doxycycline versus placebo:
The first RCT found that doxycycline was associated with gastrointestinal symptoms (including nausea and vomiting, abdominal pain, and diarrhoea) in 16/67 (24%) soldiers, unspecified dermatological problems in 22/67 (33%), cough in 21/67 (31%), and headache in 11/67 (16%) over 13 weeks. [93]

Doxycycline versus mefloquine:
The review found three RCTs that reported on adverse effects (2 in male soldiers and 1 in general travellers). [82] The review found that the proportion of drug users with any neuropsychiatric adverse event (defined as any neuropsychiatric adverse event during drug use, and not necessarily causally related to the drug) was significantly smaller with doxycycline users compared with mefloquine users; 2 RCTs: 127/220 [58%] with doxycycline *v* 152/221 [69%] with mefloquine; RR 0.84, 95% CI 0.73 to 0.96). [82] It found no significant difference between groups in the occurrence of neuropsychiatric adverse effects (defined as an adverse event for which a causal relationship is at least a possibility; 1 RCT: 6/119 [5%] with doxycycline *v* 10/134 [7%] with mefloquine; RR 0.68, 95% CI 0.25 to 1.80).

Doxycycline versus atovaquone–proguanil:
We found one systematic review (search date 2009), [82] which found one four-arm RCT [89] that reported on adverse effects. The review found no significant difference between doxycycline and atovaquone–proguanil in any adverse effects, gastrointestinal adverse outcome, or neuropsychiatric adverse outcome (any adverse outcome; 317 people: RR 0.98, 95% CI 0.88 to 1.08: gastrointestinal adverse outcome; 317 people: RR 1.01, 95% CI 0.82 to 1.25; neuropsychiatric adverse outcome; 317 people; RR 0.97, 95% CI 0.83 to 1.13). [82]

"Standard drugs" versus chloroquine–proguanil:
We found one review, [82] which pooled results for standard drugs (including doxycycline, mefloquine, and atovaquone–proguanil) versus chloroquine–proguanil for adverse effects (see harms of chloroquine–proguanil, p 15).

Doxycycline versus chloroquine–proguanil, mefloquine, or atovaquone–proguanil:
We found one RCT, [90] which compared adverse effects of prophylaxis on mood profiles (see harms of mefloquine, p 17).

Comment:

One systematic review that assessed adverse effects of atovaquone–proguanil, doxycycline, mefloquine, primaquine, and chloroquine–proguanil concluded that doxycycline and atovaquone–proguanil were the best-tolerated regimens and that mefloquine was associated with adverse neuropsychiatric outcomes. [82]

Alcohol consumption, other medication, and comorbidities can modify the effects of antimalaria drugs. [83] [84]

Clinical guide:
Doxycycline is a low-cost, once-daily drug regimen for which there is evidence of benefit, but which is contraindicated in children aged under 8 years and in pregnancy. Doxycycline protects against other travel-associated infections besides malaria. [82] Empirical evidence indicates that the monohydrate formulation of doxycycline is better tolerated by travellers than the hyclate form, which, in non-randomised studies, has been associated with a 6% withdrawal rate due to gastrointestinal adverse effects. [95]

OPTION MEFLOQUINE IN NON-PREGNANT ADULT TRAVELLERS

Malaria prevention
Compared with placebo Mefloquine is more effective than placebo at reducing malaria in non-immune Indonesian male soldiers in a malaria-endemic setting (high-quality evidence).

Compared with atovaquone–proguanil We don't know whether mefloquine and atovaquone–proguanil differ in effectiveness at preventing cases of malaria in travellers; we identified one RCT in which there were no clinical cases of malaria in either group (moderate-quality evidence).

Compared with doxycycline We don't know whether mefloquine and doxycycline differ in effectiveness at preventing clinical malaria in non-immune soldiers in a malaria-endemic setting (very low-quality evidence).

Adverse effects
Compared with atovaquone–proguanil Mefloquine may be associated with a higher rate of any adverse effects, gastrointestinal adverse effects, or neuropsychiatric adverse effects compared with atovaquone–proguanil (low-quality evidence).

Compared with doxycycline Mefloquine may be associated with a higher rate of neuropsychiatric adverse events than doxycycline. However, the significance of the result depended on the exact analysis undertaken (low-quality evidence).

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits:

Mefloquine versus placebo:
We found one systematic review (search date 2002), which identified one RCT (Indonesian soldiers, all male, non-immune) comparing three interventions: mefloquine, doxycycline, and placebo, in a malaria-endemic setting (see comment below). [96] It found that, compared with placebo, mefloquine significantly reduced smear-positive malaria (0/68 [0%] with mefloquine *v* 53/69 [77%] with placebo; OR 0.04, 95% CI 0.02 to 0.08). [96]

Mefloquine versus atovaquone–proguanil:
We found one systematic review (search date 2009), [82] which found one RCT (1013 non-immune travellers, mean exposure 2.5 weeks, various malaria-endemic destinations [63% Africa]) [97] comparing mefloquine plus placebo versus atovaquone–proguanil. It found no clinical cases of malaria among people included in the RCT.

Mefloquine versus doxycycline:
See benefits of doxycycline, p 16 .

Harms:

Mefloquine versus placebo:
The systematic review found that mefloquine significantly increased withdrawals compared with placebo (4 RCTs, 1382 people; RR 3.38, 95% CI 1.62 to 7.03). [96] We found one additional RCT that exclusively examined adverse effects of a single dose of mefloquine versus placebo. [98] It found that mefloquine increased the risk of neuropsychiatric adverse effects (mainly sleep disturbances, strange dreams, and inability to concentrate) compared with placebo (100 adult travellers; 13/59 [22%] with mefloquine *v* 3/31 [10%] with placebo; RR and CI not reported, see comment below).

Mefloquine versus atovaquone–proguanil:
In addition to the RCT that reported clinical malaria as an outcome, the review found two further RCTs, which reported on only adverse effects. [82] The review found that, compared with mefloquine, atovaquone–proguanil significantly reduced the proportion of people with any adverse effect, gastrointestinal adverse effects, neuropsychiatric adverse events, and neuropsychiatric adverse effects (any gastrointestinal effect; 1 RCT, 976 people: RR 0.72, 95% CI 0.6 to 0.85; gastrointestinal adverse effects; 1 RCT, 976 people: RR 0.54, 95% CI 0.42 to 0.70; neuropsychiatric adverse events; defined as any untoward event during treatment but which does not necessarily have a causal relationship; 1 RCT, 317 people: RR 0.86, 95% CI 0.75 to 0.99; neuropsychiatric adverse effects; defined as an adverse event for which a causal relationship between intervention and event is at least a reasonable possibility; 1 RCT, 976 people: RR 0.49, 95% CI 0.38 to 0.63). The review found that Total Mood Disturbance (TMD) scores significantly favoured atovaquone–proguanil compared with mefloquine (1 RCT, 119 people; mean difference –7.20, 95% CI –10.79 to –3.61). [82] One included RCT included both adults and children (relative numbers not reported) and one RCT had unclear reporting of adverse effects.

Mefloquine versus doxycycline:
See harms of doxycycline, p 16 .

Mefloquine versus chloroquine–proguanil:
One review [82] included one four-arm RCT (623 non-immune travellers to sub-Saharan Africa) [89] comparing four chemoprophylaxis regimens (chloroquine–proguanil, mefloquine, doxycycline, and atovaquone–proguanil) started 17 days before travel and continued for 4 weeks after return. However, it did not compare the adverse effects of mefloquine versus chloroquine–proguanil directly, but compared chloroquine–proguanil versus "standard drugs", pooling results for mefloquine, doxycycline, and atovaquone–proguanil together (see harms of chloroquine–proguanil, p 15). The RCT found that mefloquine had similar adverse-event rates to chloroquine–proguanil (severe adverse effects: 11% with mefloquine *v* 12% with chloroquine–proguanil; mild to moderate adverse effects: 42% with mefloquine *v* 45% with chloroquine–proguanil; moderate to severe neuropsychological adverse effects: 37% with mefloquine *v* 30% with chloroquine–proguanil; P value for direct comparisons not reported). [89]

Mefloquine versus chloroquine–proguanil, doxycycline, or atovaquone–proguanil:
We found one further report (547 non-immune tourists) [90] of the four-arm RCT [89] comparing chloroquine–proguanil, mefloquine, doxycycline, and atovaquone–proguanil, which reported adverse effects on mood profiles. Mood profiles were measured by the Profile of Mood States (POMS)

questionnaire (6 categories of feelings measured: tension, depression, anger, vigour, fatigue, and confusion). It found no significant difference among groups in mood impact (results presented graphically; P value not reported). In subgroup analysis, it found that women in the mefloquine group showed significantly more fatigue (P = 0.011) and confusion (P = 0.011) compared with men (results presented graphically). [90]

"Standard drugs" versus chloroquine–proguanil:
We found one review, [82] which pooled results for standard drugs (i.e., mefloquine, doxycycline, and atovaquone–proguanil) versus chloroquine–proguanil for adverse effects (see harms of chloroquine–proguanil, p 15).

Non-randomised studies:
One systematic review identified published case reports of deaths associated with included study drugs (mefloquine, atovaquone–proguanil, doxycycline, chloroquine–proguanil, and primaquine) at normal dosages. [82] It reported that it found 22 published case reports of deaths associated with the use of mefloquine at normal dosages, including five reported suicides, and no case reports of deaths attributed to any of the other drugs. It reported that this result might partly be explained by reporting bias, reflecting strong consumer concerns around the safety of mefloquine. One case control study (564 Dutch travellers between 1997–2000) found that the risk of psychiatric events was significantly higher among people taking mefloquine than in people not taking drug prophylaxis (mefloquine use: 21% in people with psychiatric events *v* 9% in controls; adjusted OR 3.5, 95% CI 1.4 to 8.7). [99] This increase was greater among women (mefloquine use: 22% in women with psychiatric events *v* 7% in controls; adjusted OR 47.1, 95% CI 3.8 to 578.6).

Comment:

The systematic review (search date 2002) [96] comparing mefloquine versus placebo has been withdrawn as it has been replaced by a more recent review (search date 2009). [82] However, the later review does not compare mefloquine versus placebo, so we have reported the earlier review here.

Mefloquine has more adverse effects than other drugs, especially in women, and these adverse effects are sometimes serious. [82] [90]

Alcohol consumption, other medication, and comorbidities can modify the effects of antimalaria drugs. [83] [84]

Clinical guide:
Mefloquine may still be an appropriate choice for those travellers who have taken it previously, without any adverse events. [82] Other factors should be considered by prescribers, in addition to tolerability: cost, ease of administration, possible drug–drug interactions, travel itinerary, and the additional protection that may be afforded by doxycycline against other infections besides malaria.

OPTION ATOVAQUONE–PROGUANIL IN NON-PREGNANT ADULT TRAVELLERS

Malaria prevention
Compared with placebo Atovaquone–proguanil may be more effective than placebo at reducing the proportion of people with malaria in Indonesian migrants with limited immunity and in non-immune Colombian soldiers in an endemic area (low-quality evidence).

Compared with chloroquine–proguanil We don't know whether atovaquone–proguanil and chloroquine–proguanil differ in effectiveness in preventing malaria in travellers (moderate-quality evidence).

Compared with mefloquine We don't know whether atovaquone–proguanil and mefloquine differ in effectiveness at preventing cases of malaria in travellers; we identified one RCT in which there were no clinical cases of malaria in either group (moderate-quality evidence).

Adverse effects
Compared with mefloquine Atovaquone–proguanil may be associated with a lower rate of any adverse effects, gastrointestinal adverse effects, or neuropsychiatric adverse effects, compared with mefloquine (low-quality evidence).

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits:

Atovaquone–proguanil versus placebo:
We found no systematic review, but found two RCTs. [100] [101] The first RCT (299 Indonesian migrants with limited immunity) found that atovaquone–proguanil significantly decreased the proportion of people with malaria at 24 weeks compared with placebo (3/150 [2%] with atovaquone–proguanil *v* 37/149 [25%] with placebo; P less than 0.001). [101] The second RCT (180 non-immune Colombian soldiers) found lower rates of malaria with atovaquone–proguanil, used

for the duration and for 1 week, after a 10- to 16-week residence in an endemic area, compared with placebo (9/120 [8%] with atovaquone–proguanil *v* 19/60 [32%] with placebo; P value not reported). [100]

Atovaquone–proguanil versus chloroquine–proguanil:
We found one systematic review (search date 2009), [82] which included one multicentre RCT (1083 travellers) [102] comparing atovaquone–proguanil versus chloroquine–proguanil, which reported clinical cases of malaria. The review found no significant difference between groups in clinical malaria (0/501 [0%] with atovaquone–proguanil *v* 3/507 [0.6%] with chloroquine–proguanil; RR 0.14, 95% CI 0.01 to 2.79). [82] However, there were only three cases of clinical malaria in the RCT, with none in the atovaquone–proguanil arm.

Atovaquone–proguanil versus mefloquine:
See benefits of mefloquine in adults, p 17 .

Harms:

Atovaquone–proguanil versus placebo:
The first RCT in migrants to Papua found that stomatitis (P less than 0.001) and back pain (P = 0.009) occurred significantly more frequently in the atovaquone–proguanil group, whereas abdominal pain (P = 0.02) and malaise (P = 0.01) occurred significantly more frequently with placebo (absolute numbers not reported). [101] Four people had severe adverse effects that were possibly drug related (3 people with abdominal pain and 1 with skin rash). [101] In the second RCT, headache was more commonly reported with atovaquone–proguanil (7% with atovaquone–proguanil *v* 3% with placebo; absolute numbers and P values not reported), as was fever (5% with atovaquone–proguanil *v* 0% with placebo; absolute numbers and P values not reported). [100]

Atovaquone–proguanil versus chloroquine–proguanil:
The systematic review [82] found two RCTs [102] [89] reporting on adverse effects, although it did not report on adverse effects of atovaquone–proguanil versus chloroquine–proguanil directly, but reported a combined analysis of "standard drugs" versus chloroquine–proguanil (see below). The multicentre RCT in travellers found no significant difference between atovaquone–proguanil and chloroquine–proguanil in the proportion of people who had one or more adverse effect (311/511 [61%] with atovaquone–proguanil *v* 329/511 [64%] with chloroquine–proguanil; RR 0.95, 95% CI 0.85 to 1.04). [102] Common adverse effects were mainly gastrointestinal (diarrhoea: 5% with atovaquone–proguanil *v* 7% with chloroquine–proguanil; mouth ulcers: 4% with atovaquone–proguanil *v* 5% with chloroquine–proguanil; abdominal pain: 3% with atovaquone–proguanil *v* 6% with chloroquine–proguanil; nausea: 2% with atovaquone–proguanil *v* 7% with chloroquine–proguanil), neuropsychiatric (strange/vivid dreams: 4% with atovaquone–proguanil *v* 3% with chloroquine–proguanil; dizziness: 3% with atovaquone–proguanil *v* 4% with chloroquine–proguanil; insomnia: 2% with atovaquone–proguanil *v* 2% with chloroquine–proguanil), and visual difficulties (2% with atovaquone–proguanil *v* 2% with chloroquine–proguanil). [102] The second RCT (623 non-immune travellers to sub-Saharan Africa) compared four chemoprophylaxis regimens (atovaquone–proguanil, chloroquine–proguanil, mefloquine, and doxycycline) started 17 days before travel and continued for 4 weeks after return. [89] It found that atovaquone–proguanil reduced severe (requiring medical advice) adverse effects compared with chloroquine–proguanil, but did not report the significance of the difference between groups (11/164 [7%] with atovaquone–proguanil *v* 19/153 [12%] with chloroquine–proguanil; significance of between-group difference not reported). It also found lower rates of mild to moderate adverse effects with atovaquone–proguanil than with chloroquine–proguanil (32% with atovaquone–proguanil *v* 45% with chloroquine–proguanil; significance of between-group difference not reported).

Atovaquone–proguanil versus mefloquine:
See harms of mefloquine in adults, p 17 .

Atovaquone–proguanil versus doxycycline:
See harms of doxycycline, p 16 .

Atovaquone–proguanil versus mefloquine, chloroquine–proguanil, or doxycycline:
We found one RCT, [90] which compared adverse effects of prophylaxis on mood profiles (see harms of mefloquine, p 17).

"Standard drugs" versus chloroquine–proguanil:
We found one review [82] that pooled results for standard drugs (including atovaquone–proguanil, mefloquine, and doxycycline) versus chloroquine–proguanil for adverse effects (see harms of chloroquine–proguanil, p 15).

Comment:

One systematic review that assessed adverse effects of atovaquone–proguanil, doxycycline, mefloquine, primaquine, and chloroquine proguanil concluded that atovaquone–proguanil and

doxycycline were the best-tolerated regimens and that mefloquine was associated with adverse neuropsychiatric outcomes. [82]

Alcohol consumption, other medication, and comorbidities can modify the effects of antimalaria drugs. [83] [84]

Clinical guide:
Atovaquone–proguanil is a high-cost, once-daily drug regimen for which there is evidence of benefit.

OPTION AMODIAQUINE IN NON-PREGNANT ADULT TRAVELLERS

We found no direct information from RCTs, cohort studies, or case control studies on the effects of amodiaquine in preventing malaria in non-pregnant adult travellers.

Note
Amodiaquine is useful to treat malaria, but there is evidence of harm with its use at current dosages to prevent malaria. Amodiaquine use is now restricted to treatment rather than prevention of malaria in resource-rich countries because of concern about adverse effects.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohort studies, or case control studies on amodiaquine in preventing malaria in non-pregnant adult travellers.

Harms: One retrospective cohort study in 10,000 British travellers taking prophylactic amodiaquine for 6 to 13 weeks reported severe neutropenia in about 1/2000 users. [103] We found 28 case reports describing liver damage or hepatitis in travellers who had taken amodiaquine for about 2 months to treat or prevent malaria. [104] [105] [106] [107] [108] [109]

Comment: Alcohol consumption, other medication, and comorbidities can modify the effects of antimalaria drugs. [83] [84]

Clinical guide:
Amodiaquine is useful to treat malaria, but there is evidence of harm with its use at current dosages to prevent malaria. Amodiaquine use is now restricted to treatment rather than prevention of malaria in resource-rich countries because of concern about adverse effects.

OPTION PYRIMETHAMINE–DAPSONE IN NON-PREGNANT ADULT TRAVELLERS

We found no direct information from RCTs, cohort studies, or case control studies on the effects of pyrimethamine–dapsone in preventing malaria in non-pregnant adult travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review or RCTs in travellers. We found no systematic review, RCTs, cohort studies, or case control studies on pyrimethamine–dapsone in preventing malaria in non-pregnant adult travellers.

Harms: One retrospective cohort study in 15,000 Swedish travellers taking pyrimethamine–dapsone reported agranulocytosis in about 1/2000 users. [110]

Comment: Alcohol consumption, other medication, and comorbidities can modify the effects of antimalaria drugs. [83] [84]

Clinical guide:
Pyrimethamine–dapsone is not currently licensed to prevent malaria. One systematic review noted that a number of older drugs and fixed-dose combinations (including pyrimethamine–dapsone) were formerly prescribed as malaria chemoprophylaxis, but they are now no longer used in travellers for this indication because of concerns around their safety. [82]

OPTION PYRIMETHAMINE–SULFADOXINE IN NON-PREGNANT ADULT TRAVELLERS

Malaria prevention
Pyrimethamine–sulfadoxine plus chloroquine compared with chloroquine–proguanil We don't know whether pyrimethamine–sulfadoxine plus chloroquine and chloroquine–proguanil differ in effectiveness at reducing the incidence of P falciparum malaria in travellers to East Africa (very low-quality evidence).

Compared with chloroquine We don't know whether pyrimethamine–sulfadoxine and chloroquine differ in effectiveness at preventing malaria in Austrian industrial workers residing in Nigeria as we found insufficient evidence from one small RCT (very low-quality evidence).

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review or RCTs of pyrimethamine–sulfadoxine alone.

Pyrimethamine–sulfadoxine plus chloroquine versus chloroquine–proguanil:
See benefits of chloroquine–proguanil in adults, p 15 .

Pyrimethamine–sulfadoxine versus chloroquine:
See benefits of chloroquine in adults, p 14 .

Harms: **Pyrimethamine–sulfadoxine plus chloroquine versus chloroquine–proguanil:**
See harms of chloroquine–proguanil in adults, p 15 .

Pyrimethamine–sulfadoxine versus chloroquine:
See harms of chloroquine in adults, p 14 .

One retrospective observational study in 182,300 US travellers taking weekly prophylactic pyrimethamine–sulfadoxine reported severe cutaneous reactions (erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis) in 24 people (1/5000–1/8000) after a mean of 3.4 weeks of use. The associated mortality was about 1/11,000 to 1/25,000 users. [110]

Comment: Alcohol consumption, other medication, and comorbidities can modify the effects of antimalaria drugs. [83] [84]

Clinical guide:
Pyrimethamine–sulfadoxine is not currently licensed in the UK for the prevention of malaria. One systematic review noted that a number of older drugs and fixed-dose combinations (including pyrimethamine–sulfadoxine) were formerly prescribed as malaria chemoprophylaxis, but they are now no longer used for travellers for this indication because of concerns around their safety. [82]

QUESTION What are the effects of antimalaria vaccines in adult and child travellers?

OPTION VACCINES IN ADULT AND CHILD TRAVELLERS

Malaria prevention
Compared with placebo We don't know whether antimalaria vaccines are more effective at reducing clinical episodes of malaria in residents of malaria-endemic settings (low-quality evidence).

Note
We found no direct information from RCTs, cohorts, or case control studies on the effects of antimalaria vaccines in preventing malaria in adult or child travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review or RCTs of antimalaria vaccines in travellers. We found three systematic reviews assessing antimalaria vaccines in residents. [111] [112] [113] The first review (search date 2006) identified two RCTs (137 people) assessing the effects of blood-stage vaccines on clinical malaria in residents of malaria-endemic regions. [111] The largest RCT (120 children aged 5–9 years) identified by the review assessed children exposed to natural challenge. It found no significant difference in episodes of clinical malaria between MSP/RESA (a blood-stage vaccine) and placebo (RR 1.64, 95% CI 0.94 to 2.85 in non-pre-treated participants; RR 1.25, 95% CI 0.71 to 2.20 in those pre-treated with pyrimethamine–sulfadoxine). The second review (search date 2006, 11 RCTs, more than 3000 people) found that one pre-erythrocytic vaccine (RTS,S) significantly reduced clinical episodes of malaria compared with placebo (2 RCTs, 1911 people; RR 0.76, 95% CI 0.66 to 0.88). [112] However, the review found no significant difference in clinical episodes of malaria between three other pre-erythrocytic stage vaccines (CS-NANP, CS102 peptide, ME-TRAP) and placebo (RRs not significant for all vaccines *v* placebo). The third review (search date 2008) found that results with SPf66 in reducing new episodes of *P falciparum* malaria were heterogeneous. [113] Overall, it found that SPf66 significantly reduced new episodes of *P falciparum* malaria compared with placebo (9 RCTs, 7409 people; RR 0.9, 95% CI 0.84 to 0.96). However, there was significant heterogeneity among RCTs (P = 0.0003). The review reported that a combined estimate may therefore not be a fair representation of the typical effect of the vaccine. As endemicity was greater in Africa than in other sites investigated, it performed a subgroup analysis by location

(Africa, Asia, or South America), which resolved the heterogeneity. It found no significant difference between SPf66 and placebo in new episodes of *P falciparum* malaria in Africa (4 RCTs, 2371 people; RR 0.98, 95% CI 0.90 to 1.07) or in Asia (1 RCT, 1221 people; RR 1.06, 95% CI 0.90 to 1.25). It found that SPf66 significantly reduced the number of first attacks with *P falciparum* in South America (4 RCTs, 3807 people; RR 0.72, 95% CI 0.63 to 0.82). Overall, it found no significant difference between SPf66 and placebo in new cases of *P vivax* malaria (5 RCTs, 5028 people in South America or Asia; RR 1.00, 95% CI 0.93 to 1.08; significant heterogeneity between RCTs in analysis). Subgroup analysis found significantly increased new cases of *P vivax* malaria with the vaccine in South America (4 RCTs, 3807 people; RR 1.16, 95% CI 1.01 to 1.32), whereas the one RCT in Asia found the opposite, with significantly reduced cases with SPf66 (1 RCT, 1221 people; RR 0.90, 95% CI 0.83 to 0.98). The review found no significant difference between groups in admission to hospital (3 RCTs, 2224 people in Africa; RR 0.99, 95% CI 0.91 to 1.08). [113]

Harms: Vaccine-related adverse effects with the blood-stage and pre-erythrocytic vaccines were mainly increased rates of local reactions (mainly injection-site pain, swelling, arm motion limitation, headache, and malaise). [111] [112] The third review reported three severe systemic adverse events in the vaccine group (2 hypertension, 1 facial oedema) and two in the placebo group (1 hypertension, 1 rash). [113] The third review also reported increases in local reactions, and also found systemic reactions (whole-body reactions including fever, headache, gastric symptoms, and dizziness) in as many as 67% of participants receiving the vaccine. [113]

Comment: **Clinical guide:**
There is currently no licensed vaccine to prevent malaria.

QUESTION What are the effects of antimalaria interventions in child travellers?

OPTION TOPICAL (SKIN-APPLIED) INSECT REPELLENTS CONTAINING DEET (DIETHYLTOLUAMIDE) IN CHILD TRAVELLERS

We found no direct information from RCTs, cohorts, or case control studies on the effects of diethyltoluamide (DEET) in preventing malaria in child travellers.

Note
Decades of experience of using DEET to prevent malaria in children have led to consensus that it is effective, but that it needs to be used with caution. There have been case reports of encephalopathic toxicity in children aged under 8 years after excessive use (not clearly defined) of topical (skin-applied) insect repellents containing DEET.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohorts, or case control studies on the effects of diethyltoluamide (DEET) in preventing malaria in child travellers.

Harms: We found 13 case reports of encephalopathic toxicity in children aged under 8 years after excessive use (not clearly defined) of topical (skin-applied) insect repellents containing DEET. [114] [115]

Comment: **Clinical guide:**
Infants and young children have thinner skin and greater surface area to mass ratio. [116] Decades of experience of using DEET to prevent malaria in children have led to consensus that it is effective, but that it needs to be used with caution. Some authors advise that ethylhexanediol should be issued as a topical (skin-applied) insect repellent in preference to DEET in children aged 1 to 8 years. [117]

OPTION ANTIMALARIA DRUGS IN CHILD TRAVELLERS

Malaria prevention
Atovaquone–proguanil compared with chloroquine–proguanil We don't know whether atovaquone–proguanil and chloroquine–proguanil differ in their effectiveness in preventing malaria in child travellers aged 2 to 17 years (moderate-quality evidence).

Note
Decades of experience of using chloroquine to prevent malaria in areas where there is no parasite resistance to chloroquine have led to the consensus that it is effective in travellers to these areas.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found one systematic review (search date 2009), [82] which included one RCT (multicentre study; 232 non-immune travellers aged 2 to 17 years) [118] comparing atovaquone–proguanil versus chloroquine–proguanil. The RCT found no cases of malaria in either arm (see comment below). We found no RCTs on the effects of other antimalaria drugs on preventing malaria in child travellers.

Harms: The RCT found no significant difference between atovaquone–proguanil and chloroquine–proguanil in one or more adverse events after about 20 to 50 days of use (most commonly diarrhoea, abdominal pain, vomiting, nausea, or oral ulceration; 39/110 [35%] with atovaquone–proguanil *v* 41/111 [37%] with chloroquine–proguanil; RR and CI not reported). [118]

Comment: The RCT was not powered to detect clinically important differences in drug efficacy. [118] Doxycycline is contraindicated in children aged under 12 years, as it may cause staining in growing teeth. [119]

Clinical guide:
Chloroquine is a low-cost drug, and decades of experience of using it to prevent malaria, in areas of no parasite resistance to the drug, have led to the consensus that it is effective in travellers to these areas, and that it is safe in children. [87]

QUESTION What are the effects of antimalaria interventions in pregnant travellers?

OPTION INSECTICIDE- TREATED NETS IN PREGNANT TRAVELLERS

Malaria prevention
Compared with no nets or untreated nets We don't know whether insecticide-treated bed nets are more effective than no bed nets or untreated bed nets at preventing clinical malaria in pregnant women resident in Africa or Thailand. Insecticide-treated nets may be more effective than no nets at preventing placental malaria in pregnant women resident in Africa (very low-quality evidence).

Pregnancy outcome
Compared with no nets or untreated nets Insecticide-treated bed nets may be more effective than no bed nets at preventing low birthweight in children born to women resident in Africa who were in their first or second pregnancy, but we don't know about children born to women resident in Africa and who have had five or more pregnancies, or about children born to women resident in Thailand. Insecticide-treated bed nets may be more effective than no bed nets or untreated bed nets at reducing fetal loss in women resident in Africa and in their first to fourth pregnancy or in any pregnancy in women resident in Thailand, but we don't know about in women resident in Africa who have had more than 4 pregnancies. Insecticide-treated bed nets may be more effective than untreated bed nets at preventing anaemia in pregnant women resident in Thailand, but we don't know about pregnant women resident in Africa (very low-quality evidence).

Note
We found no direct information from RCTs, cohorts, or case control studies on the effects of insecticide-treated bed nets in preventing malaria in pregnant travellers. Although we found no evidence specifically in pregnant travellers, it is likely that the evidence of benefit from the identified systematic review of pregnant long-term residents, and also evidence from insecticide-treated bed nets in preventing malaria in non-pregnant adults, can be generalised to pregnant women travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohort studies, or case control studies in pregnant travellers. We found one systematic review (search date 2009), which identified five RCTs in long-term residents of malaria-endemic areas. [120] Four RCTs conducted in Kenya and northern Ghana compared insecticide-treated bed nets versus no nets, and one RCT conducted in the Thai-Burmese border compared insecticide-treated bed nets versus untreated nets. The review did not perform a meta-analysis for the outcome of incidence of malaria, which was assessed in three RCTs. Although results favoured nets in the first two RCTs, differences between groups did not reach significance. The first RCT (503 pregnant women living in Kenya; first pregnancy) found no significant difference in the incidence of clinical malaria during pregnancy between insecticide-treated bed nets and no nets (OR 0.85, 95% CI 0.47 to 1.54; absolute numbers not reported). The second RCT (2991 pregnant women living in Kenya; first to fourth pregnancy) also found no significant difference in the incidence of clinical malaria during pregnancy between insecticide-treated bed nets and no nets (HR 0.72, 95% CI 0.19 to 2.75; absolute numbers not reported). The third RCT (341 pregnant women living in Thailand, followed for a mean of 16.6 weeks, at 3 sites in a malaria-endemic area) found that, at one study site, permethrin-impregnated bed nets significantly reduced the incidence of peripheral malaria parasitaemia in pregnancy compared with untreated nets (Shloklo camp: RR 0.39, 95% CI 0.37 to 0.82; absolute numbers not reported) but found no significant difference between groups at the other two sites (Bono and Maesalit camps: RR 1.1, 95% CI 0.57 to 2.12; ab-

solute numbers not reported). The review also found no significant difference in parasite densities between insecticide treated-bed nets and no nets (2 RCTs in Africa; OR 0.93, 95% CI 0.77 to 1.11; absolute numbers not reported).

In Africa, compared with no nets, insecticide-treated nets significantly reduced placental malaria in all pregnancies (any parity; 3 RCTs: RR 0.79, 95% CI 0.63 to 0.98; absolute numbers not reported), significantly reduced low birthweight in first or second pregnancy (2 RCTs: RR 0.77, 95% CI 0.61 to 0.98; absolute numbers not reported) but not in women who had five or more pregnancies (1 RCT; RR 1.12, 95% CI 0.56 to 2.24; absolute numbers not reported), and significantly reduced fetal loss in the first to fourth pregnancy (3 RCTs; RR 0.67, 95% CI 0.47 to 0.97; absolute numbers not reported), but not in women with more than 4 previous pregnancies (1 RCT: RR 1.02, 95% CI 0.17 to 6.23; absolute numbers not reported). For anaemia, results tended to favour insecticide-treated nets, but differences between groups were not significant. In Thailand, one RCT found that insecticide-treated nets significantly reduced anaemia and fetal loss in all pregnancies compared with untreated nets (anaemia: RR 0.63, 95% CI 0.42 to 0.93; absolute numbers not reported; fetal loss: 2/102 [2%] with treated nets *v* 10/64 [16%] with untreated nets; RR 0.21, 95% CI 0.05 to 0.92), but found no significant difference between groups for low birthweight (RR 1.04, 95% CI 0.52 to 2.07). [120] Of the five included RCTs, two RCTs had unclear allocation concealment and four RCTs were not blinded.

Harms: The review gave no information on adverse effects. [120]

Comment: Insecticide-treated nets have a beneficial impact on pregnancy outcome in malaria-endemic regions of Africa, when used by pregnant long-term residents. [120]

Clinical guide:
Although we found no evidence specifically in pregnant travellers, it is likely that the evidence of benefit from the identified systematic review of pregnant long-term residents, and also evidence from insecticide-treated bed nets in preventing malaria in non-pregnant adults (see bed nets in non-pregnant adults, p 8), can be generalised to pregnant women travellers. Long-lasting insecticidal nets (LLINs) are likely to have an extended duration of action compared with conventionally treated bed nets (see bed nets in non-pregnant adults). Pregnant travellers are specified as a different group because malaria is more common and more severe in pregnant women, and because antimalaria drugs may have toxic effects on the fetus. [121] Contracting malaria significantly increases the likelihood of miscarriage.

OPTION INSECTICIDE-TREATED CLOTHING IN PREGNANT TRAVELLERS

We found no direct information from RCTs, cohorts, or case control studies on the effects of insecticide-treated clothing in preventing malaria in pregnant travellers.

Note
Although we found no evidence specifically in pregnant travellers, it is likely that the evidence of benefit from insecticide-treated clothing in preventing malaria in non-pregnant adults can be generalised to pregnant women travellers.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohorts, or case control studies on the effects of insecticide-treated clothing in preventing malaria in pregnant travellers.

Harms: We found no evidence relating to pregnant travellers.

Diethyltoluamide (DEET):
See harms of topical (skin-applied) insect repellents in pregnant travellers, p 26 .

Comment: See comment on insecticide-treated bed nets in pregnant travellers, p 24 . See comment on topical (skin-applied) insect repellents in pregnant travellers., p 26

Clinical guide:
Although we found no evidence specifically in pregnant travellers, it is likely that the evidence of benefit from insecticide-treated clothing in preventing malaria in non-pregnant adults can be generalised to pregnant women travellers (see insecticide-treated clothing in non-pregnant adults, p 9).

OPTION SKIN-APPLIED INSECT REPELLENTS IN PREGNANT TRAVELLERS

We found no direct information from RCTs, cohorts, or case control studies on skin-applied insect repellents in preventing malaria in pregnant travellers.

Note

Although we found no evidence specifically in pregnant travellers, it is likely that the evidence of benefit from skin-applied insect repellents in preventing malaria in non-pregnant adults can be generalised to pregnant women travellers. However, there is inconclusive evidence regarding the safety of diethyltoluamide (DEET) in pregnant travellers. Some authors advise that only plant-derived skin-applied insect repellents are safe in pregnancy because of a potential risk of mutagenicity from DEET.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohorts, or case control studies on skin-applied insect repellents in preventing malaria in pregnant travellers.

Harms: We found little evidence in pregnant travellers.

Diethyltoluamide (DEET):
We found one case report indicating an adverse fetal outcome (mental retardation, impaired sensorimotor coordination, and craniofacial dysmorphology) in a child whose mother had applied DEET daily throughout her pregnancy. [122] One RCT in pregnant women (897 refugees in a Thai forest area of low malaria endemicity) comparing DEET (median dose 214.2 g/pregnancy) versus a cosmetic cream found no differences in weekly reporting of headache, dizziness, or nausea and vomiting over 2 to 6 months. [123] It also found no adverse effects on infant survival, growth, or development at either birth or 1 year (survival: 95% with DEET *v* 94% with cosmetic cream; P = 0.57; mean weight at 1 year: 7983 g with DEET *v* 7984 g with cosmetic cream). Some animal studies have found that DEET crosses the placental barrier. [124] Animal studies of reproductive effects of DEET are inconclusive. [125] [126]

Comment: See comment on insecticide-treated bed nets in pregnant travellers, p 24 . The RCT in refugees reported that DEET significantly increased the proportion of women reporting skin warmth (359/449 [80%] with DEET *v* 258/448 [58%] with cosmetic cream; RR 1.39, 95% CI 1.27 to 1.52), although the clinical significance of this is unclear. [123]

Clinical guide:
Although we found no evidence specifically in pregnant travellers, it is likely that the evidence of benefit from skin-applied repellents in preventing malaria in non-pregnant adults can be generalised to pregnant women travellers (see skin-applied insect repellents in non-pregnant adults, p 10). However, there is inconclusive evidence regarding the safety of DEET in pregnant travellers. Some authors advise that only plant-derived skin-applied insect repellents are safe in pregnancy because of a potential risk of mutagenicity from DEET. [117] However, we found no evidence on the effects of other repellents.

OPTION ANTIMALARIA DRUGS IN PREGNANT TRAVELLERS

Malaria prevention
Compared with no drug prophylaxis Antimalaria prophylaxis is more effective than no prophylaxis at reducing the proportion of pregnant women infected at least once in pregnant women who are resident in malaria-endemic settings (high-quality evidence).

Pregnancy outcome
Compared with no drug prophylaxis Antimalaria prophylaxis may be no more effective than no prophylaxis at reducing perinatal deaths or preterm births, or at improving mean birthweight in pregnant women resident in malaria-endemic settings (low-quality evidence).

Note
We found no direct information from RCTs, cohorts, or case control studies on the effects of antimalaria drugs in preventing malaria in pregnant travellers. Decades of experience of using chloroquine to prevent malaria, in areas of no parasite resistance to the drug, have led to the consensus that it is effective in travellers to these areas.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review or RCTs in pregnant travellers. We found one systematic review (search date 2006) of antimalaria drugs in pregnant women living in malaria-endemic settings. [127] It found that antimalaria prophylaxis significantly reduced the proportion of women infected at least

once compared with no prophylaxis (1 RCT, 337 women; AR: 5/167 [3%] with prophylaxis *v* 37/170 [22%] with no prophylaxis; RR 0.14, 95% CI 0.06 to 0.34), and significantly reduced the number of episodes of fever (1 RCT, 227 women; 21/119 [18%] with prophylaxis *v* 45/108 [42%] with no prophylaxis; RR 0.42, 95% CI 0.27 to 0.66). It found no significant difference between antimalaria prophylaxis and no prophylaxis in the proportion of perinatal deaths (4 RCTs, 2890 women; 66/1464 [4%] with prophylaxis *v* 64/1426 [4%] with no prophylaxis; RR 1.02, 95% CI 0.73 to 1.43), in the proportion of preterm births (1 RCT, 199 women; 4/102 [4%] with prophylaxis *v* 8/97 [8%] with no prophylaxis; RR 0.48, 95% CI 0.15 to 1.53), or in mean birthweight (4 RCTs, 2671 women; WMD +24 g, 95% CI –55 g to +105 g; random effects analysis).

Harms: The review gave no information about adverse effects. [127]

Chloroquine:
One RCT (1464 pregnant long-term residents of Burkina Faso) gave no information on adverse effects. [128]

Doxycycline:
Case reports found that doxycycline taken in pregnancy or while breastfeeding may damage fetal or infant bones or teeth. [86]

Mefloquine:
One RCT (339 long-term Thai residents) found that mefloquine significantly increased the proportion of women reporting dizziness compared with placebo (28% with mefloquine *v* 14% with placebo; P less than 0.005). However, it found no other significant adverse effects on the mother, the pregnancy, or on infant survival or development over 2 years' follow-up. [129]

Comment: See comment on insecticide-treated bed nets in pregnant travellers, p 24 . Mefloquine is secreted in small quantities in breast milk, but it is believed that levels are too low to harm infants. [86] Because of the potential for damage to fetal or infant bones or teeth, doxycycline is contraindicated in pregnant or breastfeeding women. [119]

Clinical guide:
Chloroquine is a low-cost drug, and decades of experience of using it to prevent malaria, in areas of no parasite resistance to the drug, have led to the consensus that it is effective in travellers to these areas, and that it is safe in pregnant women. [87]

QUESTION What are the effects of antimalaria interventions in airline pilots?

OPTION ANTIMALARIA DRUGS IN AIRLINE PILOTS

We found no direct information from RCTs, cohorts, or case control studies on the effects of antimalaria drugs in preventing malaria in airline pilots.

Note
There is no reason to suggest that evidence of benefit of atovaquone–proguanil, chloroquine, or doxycycline in other adults would not be generalisable to airline pilots. Airline pilots are specified as a different population because, as an occupational group, they are subject to health and safety legislation that is highly prescriptive about certain drugs.

For GRADE evaluation of interventions for malaria: prevention in travellers, see table, p 32 .

Benefits: We found no systematic review, RCTs, cohorts, or case control studies on the effects of antimalaria drugs in preventing malaria in airline pilots (see comment below).

Harms:

Atovaquone–proguanil:
One small crossover RCT reporting on adverse effects (24 male and female non-travelling Dutch volunteers, assessed in a hypobaric chamber) found that atovaquone–proguanil did not significantly affect vigilance, sustained attention, complex information processing, sleepiness, sleep quality, or sleep time compared with placebo. [130] No serious adverse effects were reported. There were 12 mild adverse events (including diarrhoea) with atovaquone–proguanil, and 17 adverse events with placebo (significance assessment not performed). There was one case of nosebleeding during the trial period, and one of night sweating.

Doxycycline:
One retrospective questionnaire survey (28 Israeli pilots) found that 39% experienced adverse effects from up to 2 months of doxycycline treatment (abdominal pain: 7/28 [25%]; fatigue: 5/28 [18%]; see comment below). [131]

Mefloquine:
One placebo-controlled RCT of adverse effects (23 trainee commercial pilots) found no evidence that mefloquine significantly affected flying performance after 3 weeks of treatment (mean total number of errors recorded by the instrument coordination analyser: 12.6 with mefloquine *v* 11.7 with placebo). [132] One retrospective questionnaire survey (15 Israeli non-aviator aircrew) found that 13% of respondents experienced adverse effects from mefloquine after up to 2 months of treatment (dizziness, nausea, and abdominal pain: 2/15 [13%]; abdominal discomfort: 1/15 [7%]; see comment below). [131]

Comment: One retrospective questionnaire survey (28 Israeli pilots taking doxycycline and 15 non-aviator crew taking mefloquine) found no cases of malaria at 4 weeks. [131]

Clinical guide:
There is no reason to suggest that evidence of benefit of atovaquone–proguanil, chloroquine, or doxycycline in other adults would not be generalisable to airline pilots (see question on drug prophylaxis in adults). There is evidence that atovaquone–proguanil does not harm airline pilots compared with placebo. Airline pilots are specified as a different population because, as an occupational group, they are subject to health and safety legislation that is highly prescriptive about certain drugs.

GLOSSARY

Aedes Genus of day-biting mosquitoes which transmit various infections (dengue fever, yellow fever), but not malaria.

Anopheles Genus of evening- and night-biting mosquitoes which transmit malaria.

Carbamate Class of synthetic insecticides (e.g., carbosulfan) used to treat bed nets.

Electronic buzzers Commercial devices which emit high-frequency sound waves, commonly marketed as insect repellents.

Plasmodium falciparum infection The most severe and life-threatening form of human malaria.

Plasmodium vivax infection A less severe form of human malaria, sometimes with a long incubation period of 6 to 18 months.

Biological control measures Antimosquito interventions based on modifying the local flora or fauna.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Protective efficacy $((R_1 – R_2)/R_1) \times 100$, where R_1 is the incidence of the event in the control population and R_2 is the incidence of the event in the immunised population. [133] This is the same as the relative risk reduction.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antimalaria drugs in child travellers One systematic review (search date 2009) added, which found one RCT previously reported in this *Clinical Evidence* review. [82] No new data added. Categorisation unchanged (Likely to be beneficial).

Atovaquone–proguanil in non-pregnant adult travellers One systematic review (search date 2009) added, [82] which included new analysis of data on atovaquone–proguanil versus chloroquine–proguanil, mefloquine, and doxycycline. New data added to benefits and harms sections. One follow-up report of a previously included RCT added reporting on adverse effects of prophylaxis on mood profiles. [90] New data added to harms section. Categorisation unchanged (Likely to be beneficial).

Chloroquine–proguanil in non-pregnant adult travellers One systematic review added, which found one RCT comparing chloroquine–proguanil versus atovaquone–proguanil, which was already reported in this review. [82] No new data added in benefits section, but further harms data added comparing adverse effects of chloroquine–proguanil versus three other commonly used prophylactic regimens. One follow-up report of a previously included RCT added reporting on adverse effects on mood profiles from prophylaxis. [90] New data added to harms section. Categorisation unchanged (Trade-off between benefits and harms).

Doxycycline in non-pregnant adults One systematic review added (search date 2009), which compared doxycycline versus mefloquine and pooled data. [82] New data added to benefits and harms sections. The review also found one RCT that compared adverse effects of doxycycline versus atovaquone–proguanil. Data added to the harms section.

One follow-up report of a previously included RCT added reporting on adverse effects on mood profiles of prophylaxis. [90] New data added to harms section. Categorisation unchanged (Likely to be beneficial).

Electronic mosquito repellents in non-pregnant adult travellers Option title clarified. Changed from electronic buzzers to electronic mosquito repellents. One systematic review (search date 2009) added, which found no RCTs reporting on clinical outcomes. [46] The review identified 10 field entomological studies that reported mosquitoes landing on skin as an outcome. Details of these studies added to the comments section as background data. Categorisation unchanged (Unknown effectiveness).

Insecticide-treated nets in non-pregnant adult travellers One cluster RCT in long-term residents using long-lasting insecticidal nets added. [53] Benefits and harms sections enhanced. Overall conclusions the same as before. Categorisation unchanged (Likely to be beneficial).

Insecticide-treated nets in pregnant travellers One systematic review (search date 2009) already reported in this *Clinical Evidence* review updated and new data added to benefits and harms. [120] Updated review comes to similar conclusions as before. Categorisation unchanged (Likely to be beneficial).

Mefloquine in non-pregnant adult travellers One new systematic review (search date 2009) added, which included a new meta-analysis of mefloquine versus doxycycline. [82] Data added to benefits and harms. In addition, new harms data from the review added on mefloquine versus atovaquone–proguanil. One follow-up report of a previously included RCT added reporting on effects on mood profiles. [90] New data added to harms section. New data on case reports added to harms section. [82] Categorisation unchanged (Trade-off between benefits and harms).

Primaquine in non-pregnant adult travellers One systematic review (search date 2009) added, which compared primaquine versus atovaquone–proguanil, doxycycline, and mefloquine and found no RCTs. [82] No new data added to harms or benefits. Categorisation unchanged (Likely to be ineffective or harmful).

Skin-applied chemical repellents in non-pregnant adult travellers One crossover RCT added to comments as background information, which compared four commercial skin-applied preparations versus placebo in residents and reported the effects on biting-mosquito counts. [71] No new data added to benefits or harms. Categorisation unchanged (Likely to be beneficial).

Skin-applied plant-based repellents in non-pregnant adult travellers One RCT added to comments as background information comparing a combination of a plant based repellent plus insecticide-treated net with insecticide-treated net alone in resident adults and children in the Bolivian Amazon. [73] One crossover RCT added to comments as background information, which compared four commercial skin-applied preparations versus placebo in residents and reported the effects on biting-mosquito counts. [71] No new data added to benefits or harms. Categorisation unchanged (Unknown effectiveness).

Vaccines in adult and child travellers One previously reported systematic review updated (search date 2008). [113] New data added but overall conclusions of the updated review remain the same. Categorisation unchanged (Unknown effectiveness).

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Disclaimer

TABLE **GRADE evaluation of interventions for malaria: prevention in travellers**

Important outcomes	Mortality, malaria prevention, pregnancy outcome, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of non-drug interventions to prevent malaria in non-pregnant adult travellers?									
3 (1466) [28] [48] [49]	Malaria prevention	Coil use or vapourising mat *v* no coil use or vapourising mat	2	0	0	–2	0	Very low	Note: 3 case control studies. Directness points deducted for inclusion of other repellent methods (nets, oils, creams) in analysis and for inclusion of long-term residents
4 (unclear) [52]	Mortality	Insecticide-treated nets *v* no nets or untreated nets	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results and analysis also including data on curtains. Directness points deducted for inclusion of data on children and long-term residents
6 (at least 5835) [52] [53]	Malaria prevention	Insecticide-treated nets *v* no nets or untreated nets	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results and analysis also including data on curtains. Directness points deducted for inclusion of data on children and long-term residents
4 (1135) [55] [56] [57] [58]	Malaria prevention	Insecticide-treated clothing *v* untreated clothing	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results and for inclusion of non-randomised trial. Directness points deducted for uncertainty about generalisibility of results (soldiers, refugees) and for co-intervention in 1 study (chemoprophylaxis)
2 (444) [59] [60]	Malaria prevention	Full-length clothing *v* non full-length clothing	2	–3	0	–1	+2	Very low	Note: non-randomised trial and case control study. Quality points deducted for incomplete reporting of results, unclear trial design, no baseline data, or details on possible confounders. Directness point deducted for restricted population in 1 study (air force personnel) affecting generalisability of result. Effect-size points added for OR less than 0.2
3 (9516) [63] [64] [65]	Malaria prevention	Skin-applied chemical repellents *v* no skin-applied chemical repellents	4	–2	0	–2	0	Very low	Quality points deducted for inclusion of non-randomised data and for low uptake of intervention (50–70%) in 1 RCT. Directness point deducted for limited comparators (only soap) and inclusion of data on long-term residents
What are the effects of antimalaria drug prophylaxis in non-pregnant adult travellers?									
1 (176) [80]	Malaria prevention	Primaquine *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for restricted population (soldiers)
1 (99) [81]	Malaria prevention	Primaquine *v* chloroquine	2	–1	0	–2	+1	Very low	Note: non-randomised trial. Quality point deducted for sparse data. Directness points deducted for restricted population (males) and undertaken in area of chloroquine resistance affecting generalisability of results. Effect-size point added for RR less than 0.5
1 (173) [85]	Malaria prevention	Chloroquine *v* pyrimethamine–sulfadoxine	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and unclear baseline immunity status. Directness point deducted for small number of events (no cases of clinical malaria)
1 (767) [88]	Malaria prevention	Chloroquine–proguanil *v* chloroquine plus pyrimethamine–sulfadoxine	4	–2	0	–1	0	Very low	Quality points deducted for open-label RCT and for unclear duration of follow-up. Directness point deducted for small number of events (7 in total)

Important outcomes	Mortality, malaria prevention, pregnancy outcome, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
3 (1530) [82]	Adverse effects	Chloroquine–proguanil *v* standard drugs	4	–3	0	–1	0	Very low	Quality points deducted for unclear reporting in 1 RCT, no blinding in 1 RCT, and comparison of single agent versus results pooled for three different agents. Directness point deducted for inclusion of data in children
2 (288) [93] [94]	Malaria prevention	Doxycycline *v* placebo	4	0	0	–1	+2	High	Directness point deducted for inclusion of data on migrants with limited immunity. Effect-size points added for RR less than 0.2
2 (388) [82]	Malaria prevention	Doxycycline *v* mefloquine	4	–1	0	–2	0	Very low	Quality point deducted for low level of follow-up in 1 RCT. Directness points deducted for restricted population (soldiers) and small numbers of events (1 case of malaria)
At least 2 (at least 441) [82]	Adverse effects	Doxycycline *v* mefloquine	4	0	0	–2	0	Low	Directness points deducted for restricted population (male soldiers in 2 RCTs) and significance of results dependent on exact analysis performed (based on either any event or an event for which there was a possibility of a causal relationship)
1 (137) [96]	Malaria prevention	Mefloquine *v* placebo	4	–1	0	–1	+2	High	Quality point deducted for sparse data. Directness point deducted for restricted population (male soldiers). Effect-size points added for OR less than 0.2
1 (1013) [97]	Malaria prevention	Mefloquine *v* atovaquone–proguanil	4	0	0	–1	0	Moderate	Directness point deducted for small number of events (no cases of malaria)
3 (1412) [82]	Adverse effects	Mefloquine *v* atovaquone–proguanil	4	–1	0	–1	0	Low	Quality point deducted for unclear reporting of adverse events in 1 RCT. Directness point deducted for inclusion of data in children
2 (479) [100] [101]	Malaria prevention	Atovaquone–proguanil *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for restricted population (soldiers in 1 RCT; migrants with limited immunity in 1 RCT)
1 (1083) [82]	Malaria prevention	Atovaquone–proguanil *v* chloroquine–proguanil	4	0	0	–1	0	Moderate	Directness point deducted for low number of events (3 cases of malaria in RCT)
What are the effects of antimalaria vaccines in adult and child travellers?									
At least 13 (at least 9357) [111] [112] [113]	Malaria prevention	Vaccines *v* placebo	4	0	–1	–1	0	Low	Consistency point deducted for heterogeneity among RCTs and conflicting results. Directness point deducted for inclusion of data on residents
What are the effects of antimalaria interventions in child travellers?									
1 (232) [82]	Malaria prevention	Atovaquone–proguanil *v* chloroquine–proguanil	4	0	0	–1	0	Moderate	Directness point deducted for small number of events (no cases of malaria)
What are the effects of antimalaria interventions in pregnant travellers?									
3 (3845) [120]	Malaria prevention	Insecticide-treated nets *v* no nets or untreated nets	4	–2	0	–1	0	Very low	Quality points deducted for weak methods (allocation concealment, blinding) and incomplete reporting of results. Directness point deducted for inclusion of residents

Important outcomes	Mortality, malaria prevention, pregnancy outcome, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
At least 4 (unclear) [120]	Pregnancy outcome	Insecticide-treated nets *v* no/untreated nets	4	–2	0	–1	0	Very low	Quality points deducted for weak methods (allocation concealment, blinding) and incomplete reporting of results. Directness point deducted for inclusion of residents
1 (337) [127]	Malaria prevention	Drug prophylaxis *v* no drug prophylaxis	4	0	0	–1	+2	High	Directness point deducted for inclusion of residents. Effect-size points added for RR less than 0.2
At least 4 (at least 2890) [127]	Pregnancy outcome	Drug prophylaxis *v* no drug prophylaxis	4	0	0	–2	0	Low	Directness points deducted for inclusion of residents and small number of events in 1 analysis (preterm birth)

Type of evidence: 4 = RCT; 2 = Observational study
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio